Novel sPLA$_2$ Inhibitors

Field of the Invention

This invention relates to novel indole compounds useful for Inflammatory Diseases.

Background of the Invention

The structure and physical properties of human non-pancreatic secretory phospholipase A$_2$ (hereinafter called, "sPLA$_2$") has been thoroughly described in two articles, namely, "Cloning and Recombinant Expression of Phospholipase A$_2$ Present in Rheumatoid Arthritic Synovial Fluid" by Seilhamer, Jeffrey J.; Pruzanski, Waldemar; Vadas Peter; Plant, Shelley; Miller, Judy A.; Kloss, Jean; and Johnson, Lorin K.; <u>The Journal of Biological Chemistry</u>, Vol. 264, No. 10, Issue of April 5, pp. 5335-5338, 1989; and "Structure and Properties of a Human Non-pancreatic Phospholipase A$_2$" by Kramer, Ruth M.; Hession, Catherine; Johansen, Berit; Hayes, Gretchen; McGray, Paula; Chow, E. Pingchang; Tizard, Richard; and Pepinsky, R. Blake; <u>The Journal of Biological Chemistry</u>, Vol. 264, No. 10, Issue of April 5, pp. 5768-5775, 1989; the disclosures of which are incorporated herein by reference.

It is believed that $sPLA_2$ is a rate limiting enzyme in the arachidonic acid cascade which hydrolyzes membrane phospholipids. Thus, it is important to develop compounds which inhibit $sPLA_2$ mediated release of fatty acids (e.g., arachidonic acid). Such compounds would be of value in general treatment of conditions induced and/or maintained by overproduction of $sPLA_2$; such as sepsis or rheumatoid arthritis.

It is desirable to develop new compounds and treatments for $sPLA_2$ induced diseases.

Summary of the Invention

This invention provides novel indole compounds having potent and selective effectiveness as inhibitors of mammalian $sPLA_2$.

This invention is also the use of novel indole compounds useful in the treatment and prevention of Inflammatory Diseases.

This invention is also the use of novel of indole compounds to inhibit mammalian $sPLA_2$ mediated release of fatty acids.

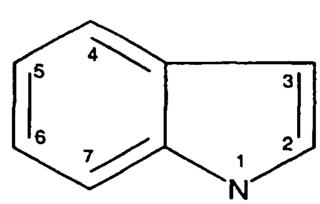
This invention is also a pharmaceutical composition containing any of the indole compounds of the invention.

I. Definitions:

The term, "Inflammatory Diseases" refers to diseases such as inflammatory bowel disease, sepsis, septic shock, adult respiratory distress syndrome, pancreatitis, trauma-induced shock, bronchial asthma, allergic rhinitis, rheumatoid arthritis, cystic fibrosis, stroke, acute bronchitis, chronic bronchitis, acute bronchiolitis, chronic bronchiolitis, osteoarthritis, gout, spondylarthropathris, ankylosing spondylitis, Reiter's syndrome, psoriatic arthropathy, enterapathric spondylitis, Juvenile arthropathy or juvenile ankylosing spondylitis, Reactive arthropathy, infectious or post-infectious arthritis, gonoccocal arthritis, tuberculous arthritis, viral arthritis, fungal arthritis, syphilitic arthritis, Lyme disease, arthritis associated with "vasculitic syndromes", polyarteritis nodosa, hypersensitivity vasculitis, Luegenec's granulomatosis, polymyalgin rheumatica, joint cell arteritis, calcium crystal deposition arthropathris, pseudo gout, non-articular rheumatism, bursitis, tenosynomitis, epicondylitis (tennis elbow), carpal tunnel syndrome, repetitive use injury (typing),

miscellaneous forms of arthritis, neuropathic joint disease (charco and joint), hemarthrosis (hemarthrosic), Henoch-Schonlein Purpura, hypertrophic osteoarthropathy, multicentric reticulohistiocytosis, arthritis associated with certain diseases, surcoilosis, hemochromatosis, sickle cell disease and other hemoglobinopathries, hyperlipoproteineimia, hypogammaglobulinemia, hyperparathyroidism, acromegaly, familial Mediterranean fever, Behat's Disease, systemic lupus erythrematosis, or relapsing polychondritis and related diseases which comprises administering to a mammal in need of such treatment a therapeutically effective amount of the compound of formula I in an amount sufficient to inhibit $sPLA_2$ mediated release of fatty acid and to thereby inhibit or prevent the arachidonic acid cascade and its deleterious products.

The term, "indole nucleus" refers to a nucleus (having numbered positions) with the structural formula (X):



(X)

The indole compounds of the invention employ certain defining terms as follows:

The term, "alkyl" by itself or as part of another substituent means, unless otherwise defined, a straight or branched chain monovalent hydrocarbon radical such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tertiary butyl, sec-butyl, n-pentyl, and n-hexyl.

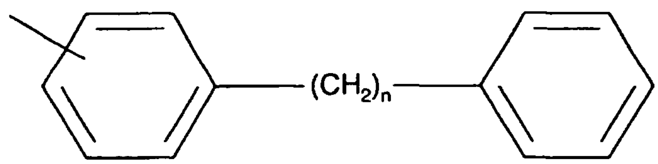
The term, "alkenyl" employed alone or in combination with other terms means a straight chain or branched monovalent hydrocarbon group having the stated number range of carbon atoms, and typified by groups such as vinyl, propenyl, crotonyl, isopentenyl, and various butenyl isomers.

The term, "hydrocarbyl" means an organic group containing only carbon and hydrogen.

The term, "halo" means fluoro, chloro, bromo, or iodo. The term, heterocyclic radical, refers to radicals derived from monocyclic or polycyclic, saturated or unsaturated, substituted or unsubstituted heterocyclic nuclei having 5 to 14 ring atoms and containing from 1 to 3 hetero atoms selected from the group consisting of nitrogen, oxygen or sulfur. Typical heterocyclic radicals are pyrrolyl, pyrrolodinyl, piperidinyl, furanyl, thiophenyl, pyrazolyl, imidazolyl, phenylimidazolyl, triazolyl, isoxazolyl, oxazolyl, thiazolyl, thiadiazolyl,

indolyl, carbazolyl, norharmanyl, azaindolyl, benzofuranyl, dibenzofuranyl, dibenzothiophenyl, indazolyl, imidazo(1.2-A)pyridinyl, benzotriazolyl, anthranilyl, 1,2-benzisoxazolyl, benzoxazolyl, benzothiazolyl, purinyl, pyridinyl, dipyridylyl. phenylpyridinyl, benzylpyridinyl, pyrimidinyl, phenylpyrimidinyl, pyrazinyl, 1,3,5-triazinyl, quinolinyl, phthalazinyl, quinazolinyl,morpholino, thiomorpholino, homopiperazinyl, tetrahydrofuranyl, tetrahydropyranyl, oxacanyl, 1,3-dioxolanyl, 1,3-dioxanyl, 1,4-dioxanyl, tetrahydrothiopheneyl, pentamethylenesulfadyl, 1,3-dithianyl, 1,4-dithianyl, 1,4-thioxanyl, azetidinyl, hexamethyleneiminium, heptamethyleneiminium, piperazinyl and quinoxalinyl.

The term, "carbocyclic radical" refers to radicals derived from a saturated or unsaturated, substituted or unsubstituted 5 to 14 membered organic nucleus whose ring forming atoms (other than hydrogen) are solely carbon atoms. Typical carbocyclic radicals are cycloalkyl, cycloalkenyl, phenyl, spiro[5.5]undecanyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenylyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (a):



(a)

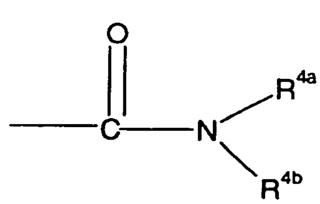
where n is a number from 1 to 8.

The term, "non-interfering substituent", refers to radicals suitable for substitution at positions 4,5,6 and/or 7 of the indole nucleus and on other nucleus substituents (as hereinafter described for Formula I), and radicals suitable for substitution on the heterocyclic radical and carbocyclic radical as defined above. Illustrative non-interfering radicals are C_1-C_8 alkyl, C_2-C_8 alkenyl, C_2-C_8 alkynyl, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C_1-C_8 alkoxy, C_2-C_8 alkenyloxy, C_2-C_8 alkynyloxy, C_2-C_{12} alkoxyalkyl, C_2-C_{12} alkoxyalkyloxy, C_2-C_{12} alkylcarbonyl, C_2-C_{12} alkylcarbonylamino, C_2-C_{12} alkoxyamino, C_2-C_{12} alkoxyaminocarbonyl, C_1-C_{12} alkylamino, C_1-C_6 alkylthio, C_2-C_{12} alkylthiocarbonyl, C_1-C_8 alkylsulfinyl, C_1-C_8 alkylsulfonyl, C_2-C_8 haloalkoxy, C_1-C_8 haloalkylsulfonyl, C_2-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, -C(O)O(C_1-C_8 alkyl), -$(CH_2)_n$-O-(C_1-C_8 alkyl), benzyloxy, phenoxy, phenylthio, -($CONHSO_2R$), -CHO, amino, amidino,

bromo, carbamyl, carboxyl, carbalkoxy, $-(CH_2)_n-CO_2H$, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, $-SO_3H$, thioacetal, thiocarbonyl, and carbonyl; where n is from 1 to 8 and R is C_1-C_8 alkyl.

The term, "organic substituent" refers to a monovalent radical consisting of carbon and hydrogen with or without oxygen, nitrogen, sulfur, halogen, or other elements. Illustrative organic substituents are C_1-C_8 alkyl, aryl, C_7-C_{14} aralkyl, C_7-C_{14} alkaryl, C_3-C_8 cycloalkyl, C_1-C_8 alkoxyalkyl and these groups substitued with halogen, $-CF_3$, -OH, C_1-C_8 alkyl, amino, carbonyl, and -CN.

The term, "acylamino acid group" is represented by the formula:



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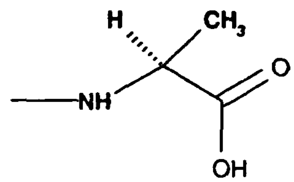
wherein R^{4a} is selected from the group consisting of H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, heteroaryl and aryl, $-CF_3$; and wherein NR^{4b} is an amino acid residue with the

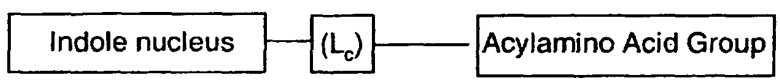
nitrogen atom being part of the amino group of the amino acid. A typical amino acid is selected from the group comprising isoleucine, valine, phenylalanine, aspartic acid, leucine, glycine, asparagine, cystein, glutamine, glutamic acid, histidine, lysine, methionine, serine, threonine, tryptophan, tyrosine and derivatives thereof. Also contemplated within the definition of amino acid is *l*-proline, *d*-proline and derivatives thereof. Also contemplated within the definition of amino acids are peptides, polypeptides and derivatives thereof.

The term "substituted group" is an organic group substituted with one or more non-interfering substituents.

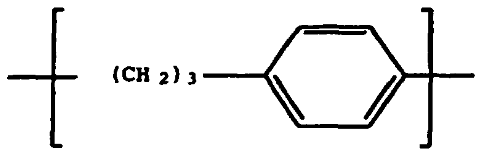
The terms, "amino acid residue" refer to the portion of the amino acid group coupled at the nitrogen atom of the amino terminus. It is the amino acid less a hydrogen atom from the amino terminus. It is further illustrated as used herein for the amino acid alanine attached at the nitrogen atom as shown below:



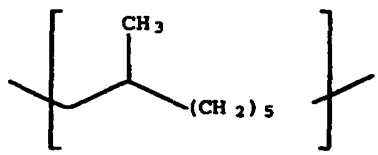
The words, "acylamino acid linker" refer to a divalent linking group symbolized as, $-(L_C)-$, which has the function of joining the 4 - position of the indole nucleus to an acylamino acid group in the general relationship:



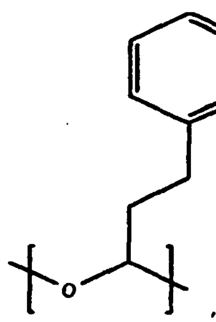
The words, "acylamino acid linker length", refer to the number of atoms (excluding hydrogen) in the shortest chain of the linking group $-(L_C)-$ that connects the 4 - position of the indole nucleus with the acylamino acid group. The presence of a carbocyclic ring in $-(L_C)-$ counts as the number of atoms approximately equivalent to the calculated diameter of the carbocyclic ring. Thus, a benzene or cyclohexane ring in the acid linker counts as 2 atoms in calculating the length of $-(L_C)-$. Illustrative acylamino acid linker groups are;



(a)



(b)



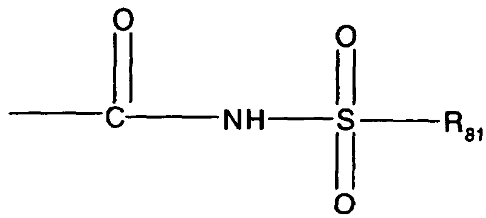
(c)

wherein, groups (a), (b) and (c) have acid linker lengths of 5, 7, and 2, respectively.

The term, "(acidic group)" means an organic group which when attached to an indole nucleus at position 5, through suitable linking atoms (hereinafter defined as the "acid linker"), acts as a proton donor capable of hydrogen bonding. Illustrative of an (acidic group) are the following:

-5-tetrazolyl,

$-SO_3H$,



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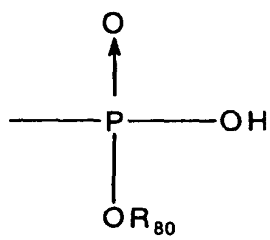

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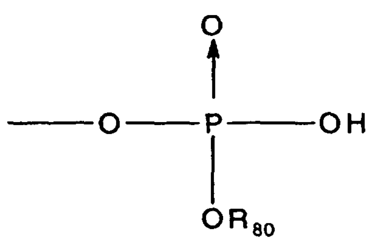

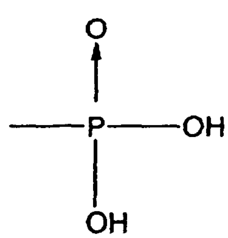

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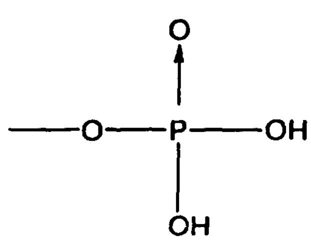

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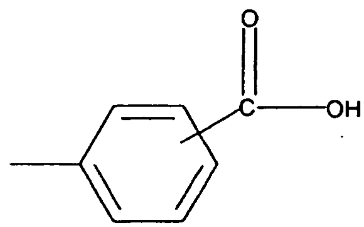

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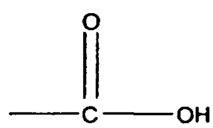

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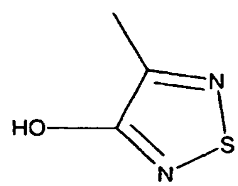
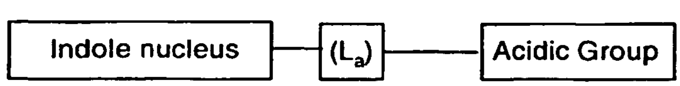


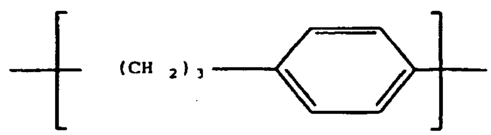
where n is 1 to 8, R_{80} is a metal or C_1-C_8 and R_{81} is an organic substituent or $-CF_3$.

The words, "acid linker" refer to a divalent linking group symbolized as, $-(L_a)-$, which has the function of joining the 5 position of the indole nucleus to an acidic group in the general relationship:

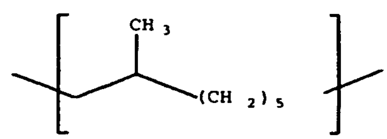


The words, "acid linker length", refer to the number of atoms (excluding hydrogen) in the shortest chain of the linking group $-(L_a)-$ that connects the 5 position of the

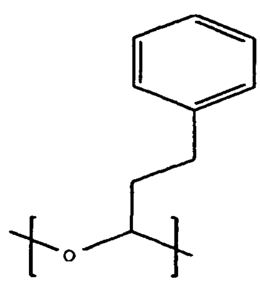
indole nucleus with the acidic group. The presence of a carbocyclic ring in $-(L_a)-$ counts as the number of atoms approximately equivalent to the calculated diameter of the carbocyclic ring. Thus, a benzene or cyclohexane ring in the acid linker counts as 2 atoms in calculating the length of $-(L_a)-$. Illustrative acid linker groups are;



(a)



(b)



(c)

wherein, groups (a), (b), and (c) have acid linker lengths of 5, 7, and 2, respectively.

The term, "amine", includes primary, secondary and tertiary amines.

The terms, "mammal" and "mammalian" include human and domesticated quadrupeds.

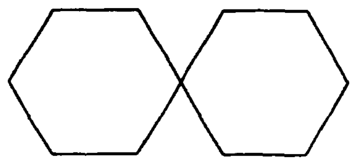
The term, "alkylene chain of 1 or 2 carbon atoms" refers to the divalent radicals, $-CH_2-CH_2-$ and $-CH_2-$.

The term, "group containing 1 to 4 non-hydrogen atoms" refers to relatively small groups which form substituents at the 2 position of the indole nucleus, said groups may contain non-hydrogen atoms alone, or non-hydrogen atoms plus hydrogen atoms as required to satisfy the unsubstituted valence of the non-hydrogen atoms, for example; (i) groups absent hydrogen which contain no more than 4 non-hydrogen atoms such as $-CF_3$, -Cl, -Br, $-NO_2$, -CN, $-SO_3$; and (ii) groups having hydrogen atoms which contain less than 4 non-hydrogen atoms such as $-CH_3$, $-C_2H_5$, and $-CH=CH_2$.

The term "oxime amide" means the radical, $-C=NOR-C(O)NH_2$

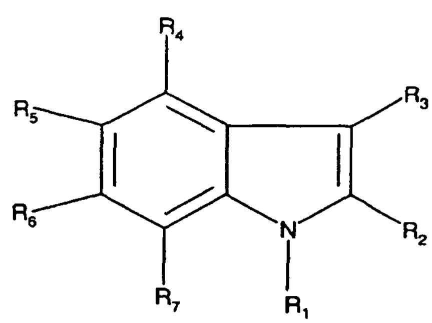
The term "thio-oxime amide" means the radical $-C=NOR-C(S)-NH_2$.

The term "spiro[5.5]undecanyl" refers to the group represented by the formula;



II. The amino acid 1H-indole Compounds of the Invention:

The present invention provides novel classes of indole compounds useful as sPLA2 inhibitors for the treatment of inflammation. Classes of indole compounds of this invention include indole glyoxylamide amino acid derivatives, indole-3-oxime amide amino acid derivatives and indole acetamide amino acid derivatives. The compounds of the invention have the general formula (I) or a pharmaceutically acceptable salt, solvate or prodrug thereof;



(I)

wherein ;

R_1 is selected from groups (a), (b), and (c) wherein;

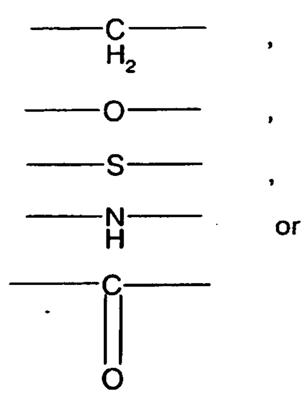
(a) is C_7-C_{20} alkyl, C_7-C_{20} haloalkyl, C_7-C_{20} alkenyl, C_7-C_{20} alkynyl, carbocyclic radical, or heterocyclic radical, or

(b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

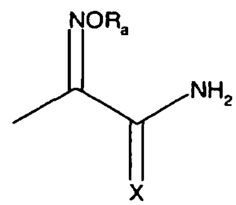
(c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a) or (b);

R_2 is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

R_3 is $-(L_3)-$ Z, where $-(L_3)-$ is a divalent linker group selected from a bond or a divalent group selected from:



and Z is selected from an oxime amide or oxime thioamide group represented by the formulae,



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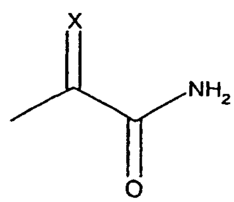

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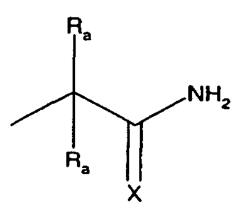


wherein X is oxygen or sulfur, R_a is independently selected from hydrogen, C_1-C_8 alkyl, aryl, C_1-C_8 alkaryl, C_1-C_8 alkoxy, aralkyl and -CN;

R_4 is the group, $-(L_c)-$(acylamino acid group); wherein $-(L_c)-$, is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

R_5 is selected from hydrogen, a non-interfering substituent, or the group, $-(L_a)-$(acidic group); wherein $-(L_a)-$, is an acid linker having an acid linker length of 1 to 8.

R_6 and R_7 are selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s), heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

Preferred Subgroups of Compounds of Formula (I):
Preferred R_1 substituents:

A preferred subclass of compounds of formula (I) are those where for R_1 the divalent linking group $-(L_1)-$ is a group represented by any one of the following formulae (Ia), (Ib), (Ic), (Id), (Ie), or (If):

$-CH_2-$, (Ia)

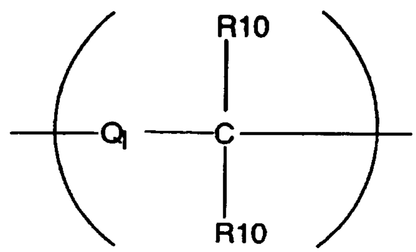
$-O-$, (Ib)

$-S-$, (Ic)

$-NH-$ or (Id)

$-C(=O)-$ (Ie)

or

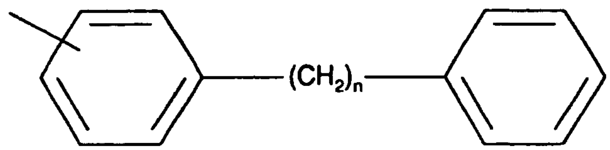


(If)

where Q_1 is a bond or any of the divalent groups (Ia), (Ib), (Ic), (Id), (Ie), and (If) and each R_{10} is independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl or C_{1-8} alkoxy.

Particularly preferred as the linking group $-(L_1)-$ of R_1 is an alkylene chain of 1 or 2 carbon atoms, namely, $-(CH_2)-$ or $-(CH_2-CH_2)-$.

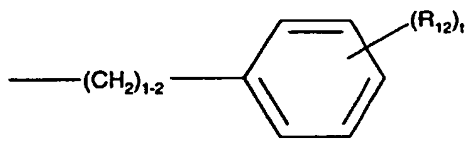
The preferred group for R_{11} is a substituted or unsubstituted group selected from the group consisting of C_5-C_{14} cycloalkyl, C_5-C_{14} cycloalkenyl, phenyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenylyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (a);



(a)

where n is a number from 1 to 8.

Particularly preferred are compounds wherein for R_1 the combined group $-(L_1)-R_{11}$ is selected from the group consisting of



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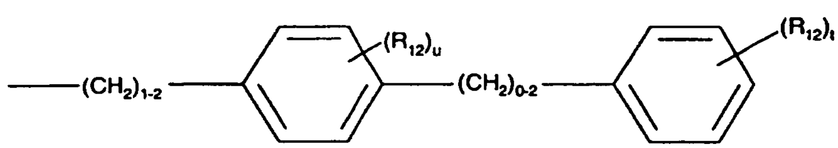
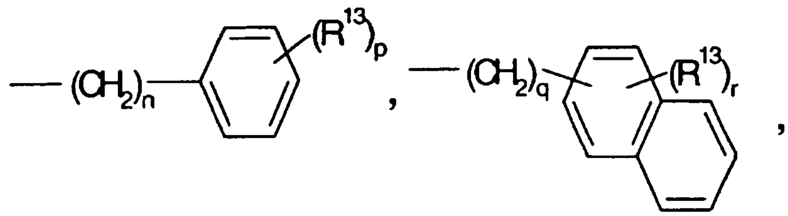
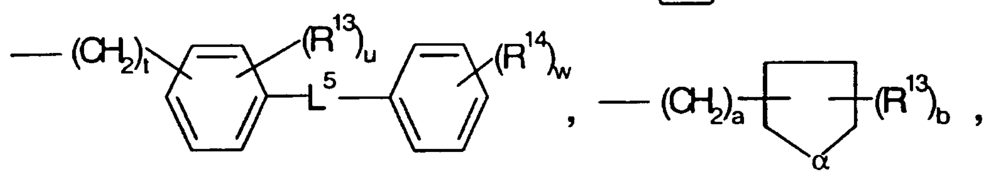
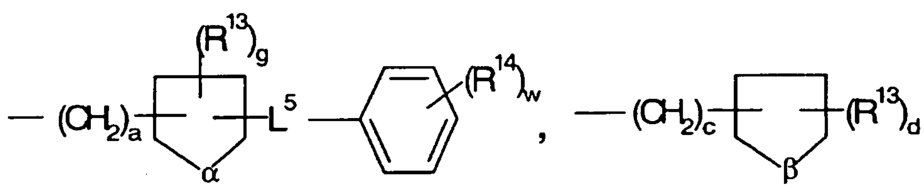


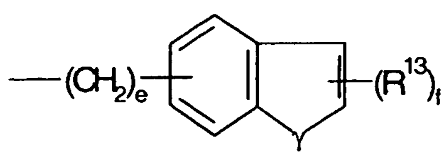
where R_{12} is a radical independently selected from halo, C_1-C_8 alkyl, C_1-C_8 alkoxy, -S-(C_1-C_8 alkyl), -O-(C_1-C_8 alkyl) and C_1-C_8 haloalkyl where t is a number from 0 to 5 and u is a number from 0 to 4 is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a) or (b).

Preferred for R_{11} is $-(CH_2)m-R^{12}$ wherein m is an integer from 1 to 6, and R^{12} is (d) a group represented by the formula:







or 

wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to C_8 haloalkyl, α is an oxygen atom or a sulfur atom, L^5 is a bond, $-(CH_2)v-$,

-C=C-, -CC-, -O-, or -S-, v is an integer from 0 to 2, β is $-CH_2-$ or $-(CH_2)_2-$, γ is an oxygen atom or a sulfur atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer

from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of C_1 to C_6 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 haloalkyloxy, C_1 to C_8 haloalkyl, aryl, and a halogen.

Preferred R_2 substituents:

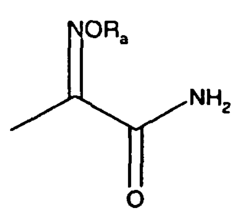
R_2 is preferably selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, -O-(C_1-C_3 alkyl),

-S-(C_1-C_3 alkyl), -C_3-C_4 cycloalkyl -CF_3, halo, -NO_2, -CN, -SO_3. Particularly preferred R_2 groups are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, -CF_3, -Cl, -Br, or -O-CH_3.

Preferred R_3 substituents:

A preferred subclass of compounds of formula (I) are those wherein X is oxygen.

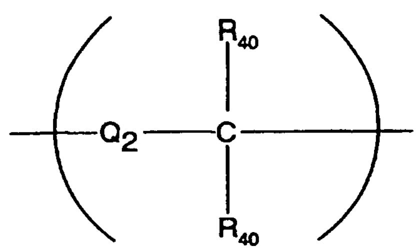
Another preferred subclass of compounds of formula (I) are those wherein Z is an oxime amide group.



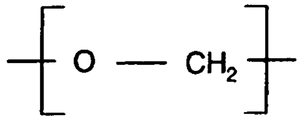
Also preferred are compounds of formula (I) wherein R_3 is an oxime amide group and R_a is hydrogen, methyl or ethyl. For the group R_3 it is preferred that the linking group $-(L_3)-$ be a bond.

Preferred R_4 substituents:

Another preferred subclass of compounds of formula (I) are those wherein R_4 is a substituent having an acylamino acid linker with an acylamino acid linker length of 2 or 3 and the acylamino acid linker group, $-(L_c)-$, for R_4 is selected from a group represented by the formula;



where Q_2 is selected from the group $-(CH_2)-$, $-O-$, $-NH-$, $-C(O)-$, and $-S-$, and each R_{40} is independently selected from hydrogen, C_1-C_8 alkyl, aryl, C_1-C_8 alkaryl, C_1-C_8 alkoxy, aralkyl, and halo. Most preferred are compounds where the acylamino acid linker, $-(L_c)-$, for R_4 is selected from the specific groups;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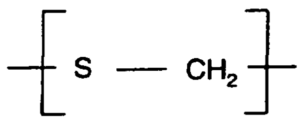
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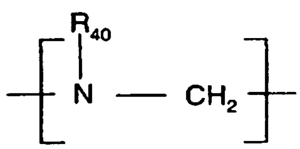
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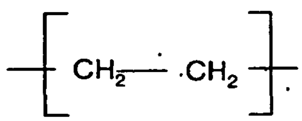
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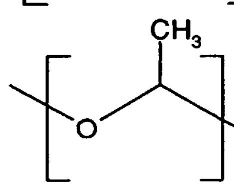
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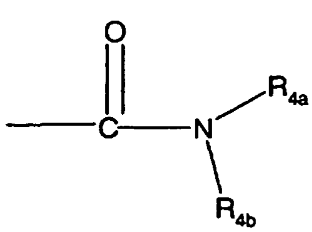
where R_{40} is hydrogen or C_1 -C_8 alkyl.

Preferred as the (acylamino acid group) in the group R_4 is the group: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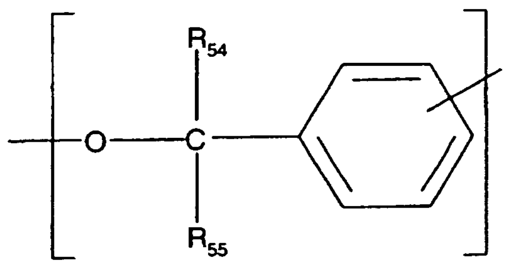
wherein R^{4a} is selected from the group consisting of H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, heteroaryl and aryl; and wherein NR^{4b} is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. A preferred R^{4a} group is the group hydrogen (H). A preferred source of amino acid residue is the amino acid group selected from the group comprising isoleucine, valine, phenylalanine, aspartic acid, leucine, glycine and isomers and derivatives thereof. A salt or a prodrug derivative of the (acylamino acid group) is also a suitable substituent.

Particularly preferred are R^{4b} groups that combine with the nitrogen atom to represent amino acid residues from the amino acid groups selected from: glycine, glycine methyl ester, L-alaninie, L-alanine methylester, L-leucine, L-leucine methyl ester, L-aspartic acid, L-aspartic acid dimethyl ester, L-phenyl alanine, L-phenylalanine methyl ester, malonic acid, malonic acid dimethylester, L- valine, L-valine methyl ester, L-isoleucine, L-isoleucine methyl ester, or salt, and derivatives thereof.

Preferred R_5 Substitu nts:

Preferred acid linker, $-(L_a)-$, for R_5 is selected from the group consisting of;



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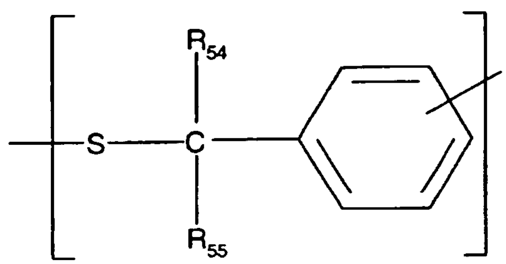

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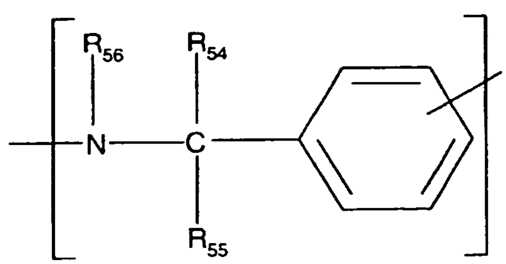

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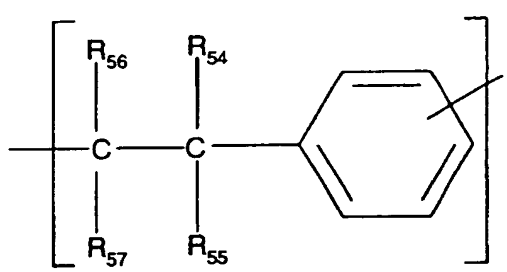

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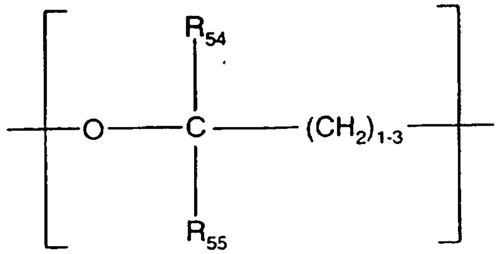

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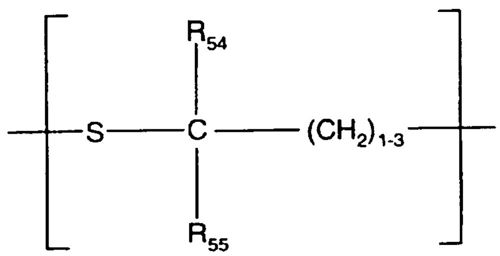

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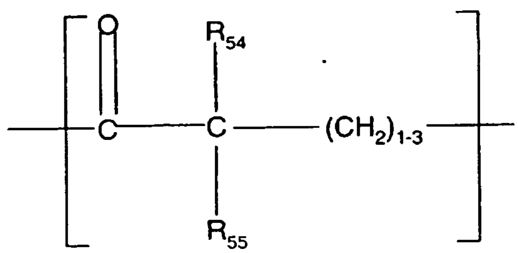

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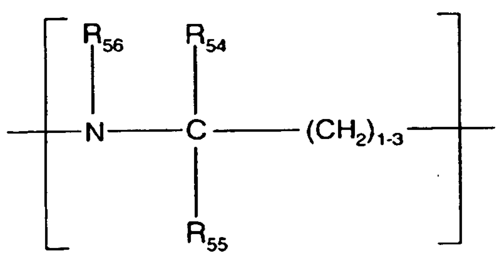

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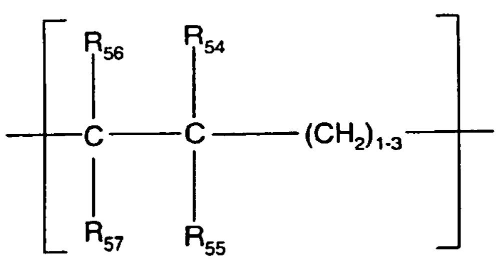


,

wherein R_{54}, R_{55}, R_{56} and R_{57} are each independently hydrogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, aryl, C_1-C_8 alkoxy, or halo. Preferred (acidic group) for R_5 is selected from the group consisting of $-CO_2H$, $-SO_3H$ and $-P(O)(OH)_2$.

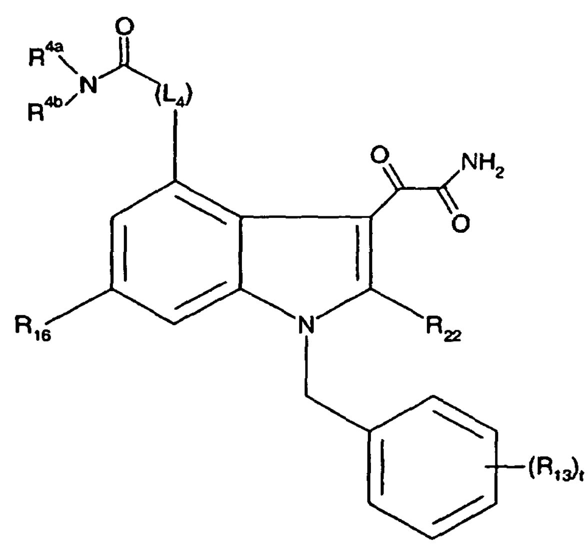
Preferred R_6 and R_7 substituents:

Another preferred subclass of compounds of formula (I) are those wherein for R_6 and R_7 the non-interfering substituent is independently methyl, ethyl, propyl, isopropyl, thiomethyl, -O-methyl, C_4-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C_1-C_6 alkoxy, C_2-C_6 alkenyloxy, C_2-C_6 alkynyloxy, C_2-C_{12} alkoxyalkyl, C_2-C_{12} alkoxyalkyloxy, C_2-C_{12} alkylcarbonyl, C_2-C_{12} alkylcarbonylamino, C_2-C_{12} alkoxyamino, C_2-C_{12} alkoxyaminocarbonyl, C_1-C_{12} alkylamino, C_1-C_6 alkylthio, C_2-C_{12} alkylthiocarbonyl, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, C_2-C_6 haloalkoxy, C_1-C_6 haloalkylsulfonyl, C_2-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, $-C(O)O(C_1$-C_6 alkyl), $-(CH_2)_n$-O-(C_1-C_6 alkyl), benzyloxy, phenoxy, phenylthio, $-(CONHSO_2R)$, -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, $-(CH_2)_n-CO_2H$, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino,

iodo, nitro, phosphono, $-SO_3H$, thioacetal, thiocarbonyl, and carbonyl; where n is from 1 to 8.

Most preferred as non-interfering substituents are methyl, ethyl, propyl, and isopropyl.

Preferred compounds of the invention are those having the general formula (II), or a pharmaceutically acceptable salt, solvate or prodrug derivative thereof;

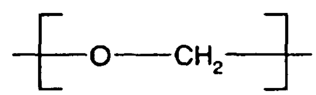


(II)

wherein ;

R_{22} is selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, $-CF_3$, -Cl, -Br, or $-O-CH_3$;

wherein R^{4a} is selected from the group consisting of H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, heteroaryl and aryl; and wherein NR^{4b} is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. A preferred R^{4a} group is the group hydrogen (H); and -(L_4)- is a divalent group selected from;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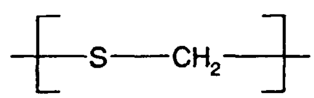
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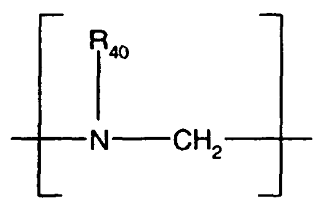
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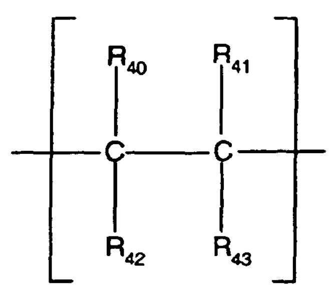
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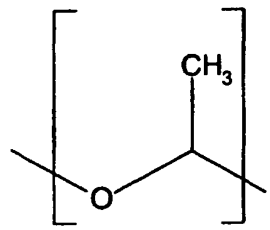


where R_{40}, R_{41}, R_{42}, and R_{43} are each independently selected from hydrogen or C_1-C_8 alkyl.

R_{16} is selected from hydrogen, C_1-C_8 alkyl, C_1-C_8 alkoxy, C_1-C_8 alkylthio C_1-C_8 haloalkyl, C_1-C_8 hydroxyalkyl, and halo.

R_{13} is selected from hydrogen and C_1-C_8 alkyl, C_1-C_8 alkoxy, -S-(C_1-C_8 alkyl), C_1-C_8 haloalkyl, C_1-C_8, phenyl, halophenyl, hydroxyalkyl, and halo, and t is an integer from 0 to 5.

Preferred specific compounds (and all pharmaceutically acceptable salts, solvates and prodrug derivatives thereof) which are illustrative of the compounds of the invention are as follow:

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine ;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine methyl ester;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine;

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester; and

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine.

The salts of the above indole compounds represented by formulae (I) and (II) are an additional aspect of the invention. In those instances where the compounds of the invention possess acidic or basic functional groups various salts may be formed which are more water soluble and physiologically suitable than the parent compound. Representative pharmaceutically acceptable salts, include but are not limited to, the alkali and alkaline earth salts such as lithium, sodium, potassium, calcium, magnesium, aluminum and the like. Salts are conveniently prepared from the free acid by treating the acid in solution with a base or by exposing the acid to an ion exchange resin.

Included within the definition of pharmaceutically acceptable salts are the relatively non-toxic, inorganic and organic base addition salts of compounds of the present invention, for example, ammonium, quaternary ammonium, and amine cations, derived from nitrogenous bases of sufficient basicity to form salts with the compounds of this invention (see, for example, S. M. Berge, *et al.*, "Pharmaceutical Salts," J. Phar. Sci., 66: 1-19 (1977)). Moreover, the basic group(s) of the compound of the invention may be reacted with suitable organic or inorganic acids to form salts such as acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate,

bitartrate, borate, bromide, camsylate, carbonate, chloride, clavulanate, citrate, chloride, edetate, edisylate, estolate, esylate, fluoride, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, bromide, chloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, malseate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, oleate, oxalate, palmitate, pantothenate, phosphate, polygalacturonate, salicylate, stearate, subacetate, succinate, tannate, tartrate, tosylate, trifluoroacetate, trifluoromethane sulfonate, and valerate.

Certain compounds of the invention may possess one or more chiral centers and may thus exist in optically active forms. Likewise, when the compounds contain an alkenyl or alkenylene group there exists the possibility of cis- and trans- isomeric forms of the compounds. The R- and S- isomers and mixtures thereof, including racemic mixtures as well as mixtures of cis- and trans- isomers, are contemplated by this invention. Additional asymmetric carbon atoms can be present in a substituent group such as an alkyl group. All such isomers as well as the mixtures thereof are intended to be included in the invention. If a particular stereoisomer is desired, it can be prepared by methods well known in the art by using stereospecific

reactions with starting materials which contain the asymmetric centers and are already resolved or, alternatively by methods which lead to mixtures of the stereoisomers and subsequent resolution by known methods. For example, a racemic mixture may be reacted with a single enantiomer of some other compound. This changes the racemic form into a mixture of diastereomers and diastereomers, because they have different melting points, different boiling points, and different solubilities can be separated by conventional means, such as crystallization.

Prodrugs are derivatives of the compounds of the invention which have chemically or metabolically cleavable groups and become by solvolysis or under physiological conditions the compounds of the invention which are pharmaceutically active in vivo. Derivatives of the compounds of this invention have activity in both their acid and base derivative forms, but the acid derivative form often offers advantages of solubility, tissue compatibility, or delayed release in a mammalian organism (see, Bundgard, H., Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985). Prodrugs include acid derivatives well known to practitioners of the art, such as, for example, esters prepared by reaction of the parent acidic compound with a suitable alcohol, or amides

prepared by reaction of the parent acid compound with a suitable amine. Simple aliphatic or aromatic esters derived from acidic groups pendent on the compounds of this invention are preferred prodrugs. In some cases it is desirable to prepare double ester type prodrugs such as (acyloxy) alkyl esters or ((alkoxycarbonyl)oxy)alkyl esters. Particularly preferred esters as prodrugs are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, morpholinoethyl, and N,N-diethylglycolamido.

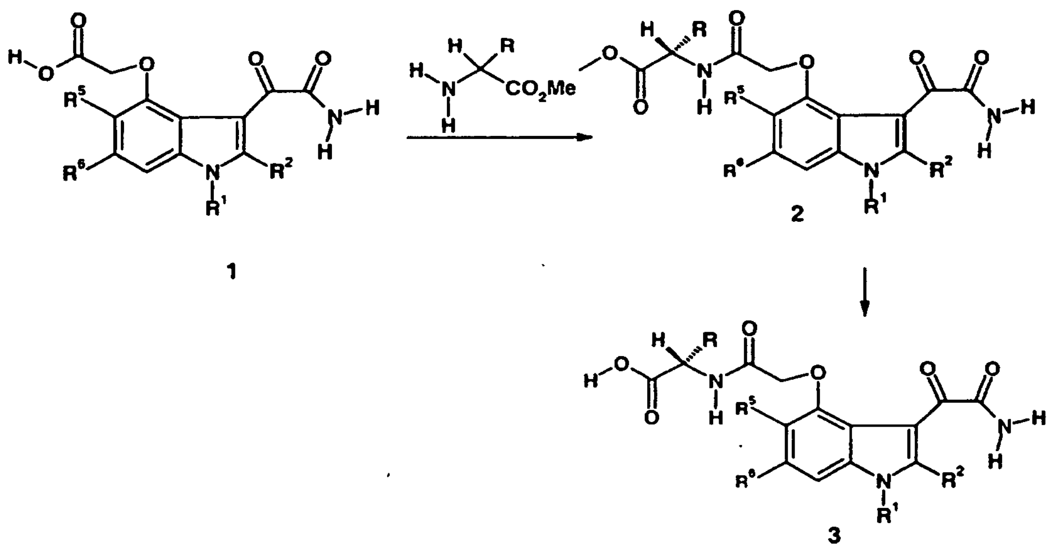
N,N-diethylglycolamido ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) with 2-chloro-N,N-diethylacetamide (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA; Item No. 25,099-6).

Morpholinylethyl ester prodrugs may be prepared by reaction of the sodium salt of a compound of Formula (I) (in a medium such as dimethylformamide) 4-(2-chloroethyl)morpholine hydrochloride (available from Aldrich Chemical Co., Milwaukee, Wisconsin USA, Item No. C4,220-3).

a) The 1H-indole-3-glyoxylamide amino derivative compounds of the invention are prepared by room temperature base catalyzed condensation of the amino acid protected at the acid terminus by protecting group

known in the literature but preferably as the methyl ester with the 1H-indole-3-glyoxylamide acid derivative compound of formula (1) as shown in Scheme I:

Scheme 1



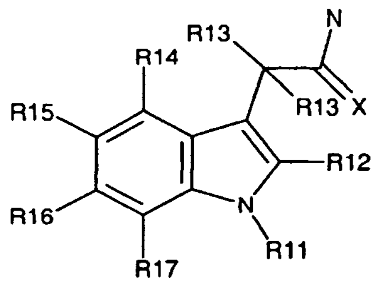
Typically, the condensation or coupling is performed in a solvent such a dimethyl formamide, tetrahydrofuran or aqueous mixtures of the like. In general protic solvents are preferred for the purpose of this invention. The reaction is catalyzed by a base including weak organic or inorganic bases. Organic bases such as collidine are preferred. The reaction is also preferably run in the presence of agents that retard or reduce racemization of the amino acid or its

derivative, such as for example, benzotriazolyl-N-oxy-tris(dimethylamino)phosphonium hexafluorophosphate. Upon completion of the reaction, the mixture is concentrated in vacuo. The resulting product mixture is chromatographed to obtain the target compound.

One of skill in the art is aware that the derivatives of the acid such as the acid salt or the methyl ester of the acid, can be reacted with the amino acid or derivatives thereof to obtain the protected compound 2 or a corresponding derivative. Such methods are well known in the arts and can be found in reference texts such as for example J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985, and R. C. Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989. The protected compounds of formula (2) are also useful $sPLA_2$ inhibitors and are also compounds of this invention.

b) 1H-indole-3-acetamide amino acid derivative $sPLA_2$ inhibitors are similarly prepared by condensation of the protected amino acid with the 1H-indole-3-acetamide $sPLA_2$ inhibitor. The 1H-indole-3-acetamide $sPLA_2$ inhibitors and methods of making them are set out in U.S. Patent No. 5,684,034, the entire disclosure of which is incorporated herein by reference. Indole-3-acetamide

amino acid derivative sPLA2 inhibitors of this invention are represented by compounds of formula (IIb), and pharmaceutically acceptable salts and prodrug derivatives thereof,



(IIb)

wherein ;

X is oxygen or sulfur;

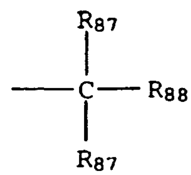
R_{11} is selected from groups (i), (ii) (iii) and (iv) where;

(i) is C_6-C_{20} alkyl, C_6-C_{20} alkenyl, C_6-C_{20} alkynyl, C_6-C_{20} haloalkyl, C_4-C_{12} cycloalkyl, or

(ii) is aryl or aryl substituted by halo, nitro, -CN, -CHO, -OH, -SH, C_1-C_{10} alkyl, C_1-C_{10} alkylthio, C_1-C_{10} alkoxyl, carboxyl, amino, or hydroxyamino; or

(iii) is $-(CH_2)_n-(R_{80})$, or $-(NH)-(R_{81})$, where n is 1 to 8, and R_{80} is a group recited in (i), and R_{81} is selected from a group recited in (i) or (ii);

(iv) is



where R_{87} is hydrogen or C_1-C_{10} alkyl, and R_{88} is selected from the group; phenyl, naphthyl, indenyl, and biphenyl, unsubstituted or substituted by halo, -CN, -CHO, -OH, -SH, C_1-C_{10} alkylthio, C_1-C_{10} alkoxyl, phenyl, nitro, C_1-C_{10} alkyl, C_1-C_{10} haloalkyl, carboxyl, amino, hydroxyamino; or a substituted or unsubstituted 5 to 8 membered heterocyclic ring;

R_{12} is halo, C_1-C_2 alkylthio, C_1-C_2 alkyl, C_1-C_2 alkyaryl or C_1-C_2 alkoxy;

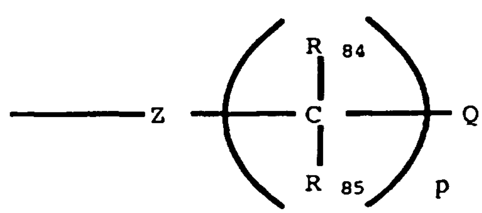
each R_{13} is independently hydrogen, halo, or methyl;

R^{14} is the group $-L_c-$[acylamino acid], wherein the acylamino acid group is $-C(O)-NR^{14a}R^{14b}$ wherein R^{14a} is selected from the group consisting of H, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, heteroaryl; and $-L_c-$ is as defined *supra*, and wherein NR^{14b} is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. Most preferred are compounds of formula II wherein the group R^{14a} is a hydrogen atom (H). A preferred source of the amino acid residue NR^{14b} is an amino acid selected from the group comprising isoleucine, valine, phenylalanine,

aspartic acid, leucine, glycine and isomers and derivatives thereof;

R_{15} is selected from hydrogen, a non-interfering substituent, or the group, -(L_a)-(acidic group); wherein -(L_a)-, is an acid linker having an acid linker length of 1 to 8;

R_{16} and R_{17} are each independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} alkenyl, C_1-C_{10} alkynyl, C_3-C_8 cycloalkyl, aryl, aralkyl, or any two adjacent hydrocarbyl groups in the set R_{15}, R_{16}, and R_{17}, combine with the ring carbon atoms to which they are attached to form a 5 or 6 membered substituted or unsubstituted carbocyclic ring; or C_1-C_{10} haloalkyl, C_1-C_{10} alkoxy, C_1-C_{10} haloalkoxy, C_4-C_8 cycloalkoxy, phenoxy, halo, hydroxy, carboxyl, -SH, -CN, C_1-C_{10} alkylthio, arylthio, thioacetal, -C(O)O(C_1-C_{10} alkyl), hydrazide, hydrazino, hydrazido, -NH_2, -NO_2, -$NR_{82}R_{83}$, and -C(O)$NR_{82}R_{83}$, where, R_{82} and R_{83} are independently hydrogen, C_1-C_{10} alkyl, C_1-C_{10} hydroxyalkyl, or taken together with N, R_{82} and R_{83} form a 5- to 8-membered heterocyclic ring; or a group having the formula;



where,

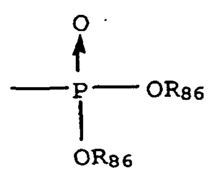
R_{84} and R_{85} are each independently selected from hydrogen, C_1-C_{10} alkyl, hydroxy, or R_{84} and R_{85} taken together are =O;

p is 1 to 5,

Z is a bond, -O-, -N(C_1-C_{10} alkyl)-, -NH-, or -S-;

and

Q is -CON($R_{82}R_{83}$), -5-tetrazolyl, $-SO_3H$,



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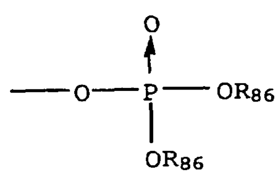

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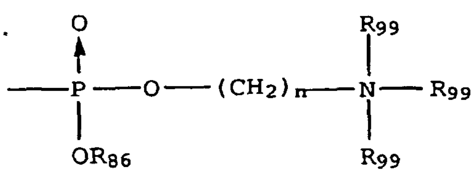

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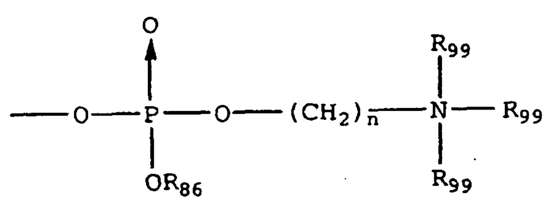

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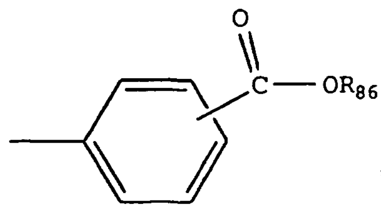

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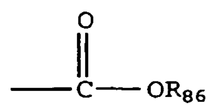

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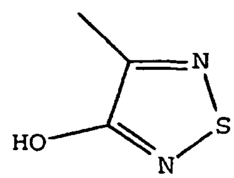
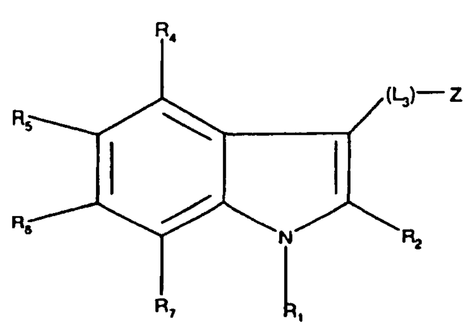


;

where n is 1 to 8, R_{86} is independently selected from hydrogen, a metal, or C_1-C_{10} alkyl, and R_{99} is selected from hydrogen or C_1-C_{10} alkyl.

c) Indole-3-Oxime amide compounds of the invention are represented by compounds of formula (III) or a pharmaceutically acceptable salt, solvate or prodrug thereof;



wherein ;

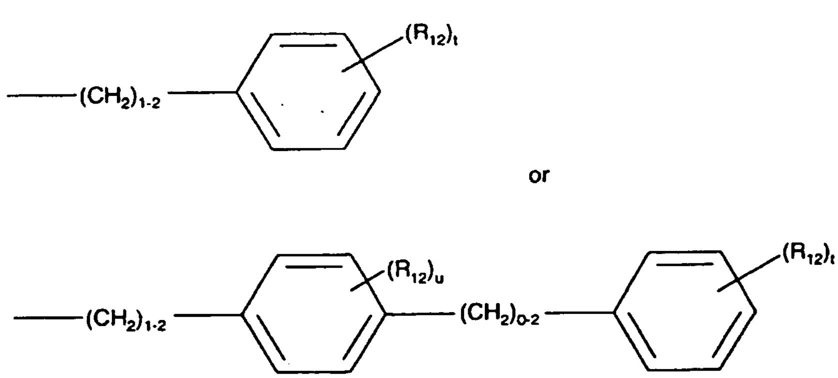
R_1 is selected from groups (a), (b), and (c) wherein;

(a) is C_7-C_{20} alkyl, C_7-C_{20} haloalkyl, C_7-C_{20} alkenyl, C_7-C_{20} alkynyl, carbocyclic radical, or heterocyclic radical, or

(b) is a member of (a) substituted with one or more independently selected non-interfering substituents; or

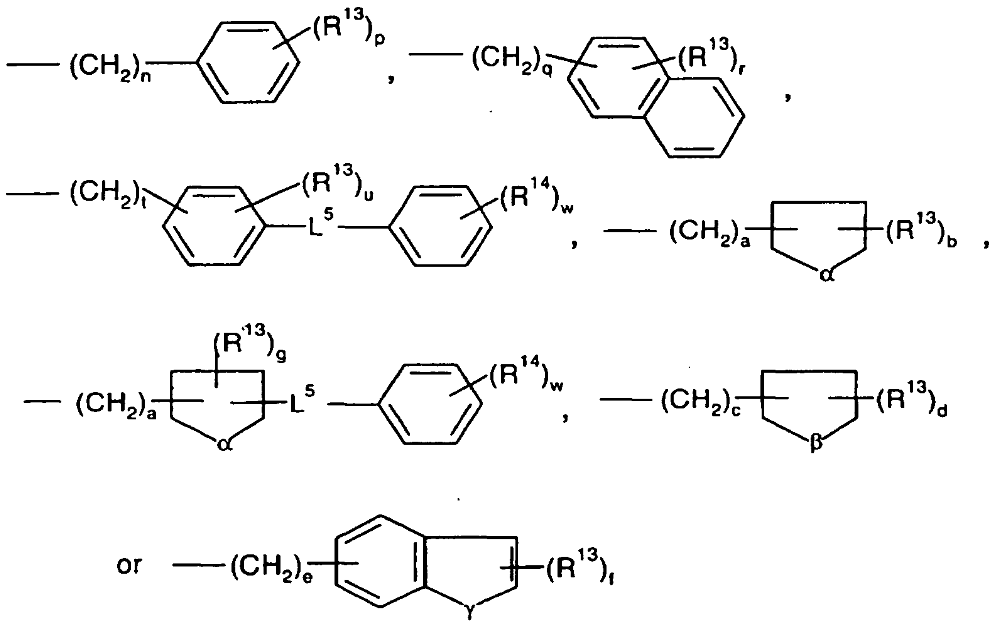
(c) is the group $-(L_1)-R_{11}$; where, $-(L_1)-$ is a divalent linking group of 1 to 8 atoms and where R_{11} is a group selected from (a) or (b).

Particularly preferred are compounds wherein for R_1 the combined group $-(L_1)-R_{11}$ is selected from the group consisting of



where R_{12} is a radical independently selected from halo, C_1-C_8 alkyl, C_1-C_8 alkoxy, -S-(C_1-C_8 alkyl), -O-(C_1-C_8 alkyl) and C_1-C_8 haloalkyl where t is a number from 0 to 5 and u is a number from 0 to 4.

Also preferred for R_{11} is $-(CH_2)m-R^{12}$ wherein m is an integer from 1 to 6, and R^{12} is (d) a group represented by the formula:

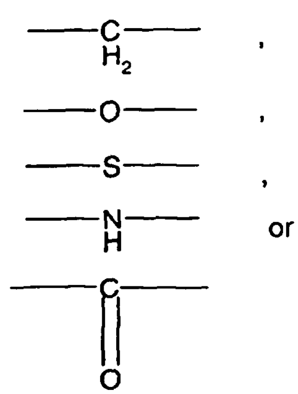


wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to

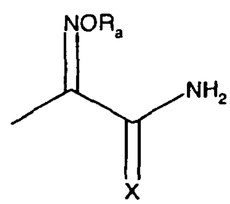
C_8 haloalkyl, α is an oxygen atom or a sulfur atom, L^5 is a bond, $-(CH_2)v-$, $-C=C-$, $-CC-$, $-O-$, or $-S-$, v is an integer from 0 to 2, β is $-CH_2-$ or $-(CH_2)_2-$, γ is an oxygen atom or a sulfur atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of C_1 to C_6 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 haloalkyloxy, C_1 to C_8 haloalkyl, aryl, and a halogen.

R_2 is hydrogen, or a group containing 1 to 4 non-hydrogen atoms plus any required hydrogen atoms;

$-(L_3)-Z$, is the group where $-(L_3)-$ is a divalent linker group selected from a bond or a divalent group selected from:



and Z is selected from an oxime amide or oxime thioamide group represented by the formulae,



wherein, X is oxygen or sulfur; and R_a is selected from hydrogen, C_1-C_8 alkyl, aryl, C_1-C_8 alkaryl, C_1-C_8 alkoxy, aralkyl and -CN;

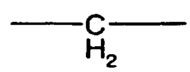
R_4 is the group, -(L_c)-(acylamino acid group); wherein -(L_c)-, is an acylamino acid linker having an acylamino acid linker length of 1 to 8;

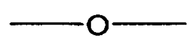
R_5 is selected from hydrogen, a non-interfering substituent, or the group, -(L_a)-(acidic group); wherein -(L_a)-, is an acid linker having an acid linker length of 1 to 8.

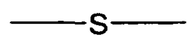
R_6 and R_7 are selected from hydrogen, non-interfering substituent, carbocyclic radical, carbocyclic radical substituted with non-interfering substituent(s), heterocyclic radicals, and heterocyclic radical substituted with non-interfering substituent(s).

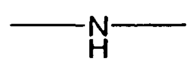
Preferred Subgroups of Compounds of Formula (III):
Preferred R_1 substituents:

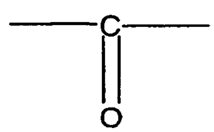
A preferred subclass of compounds of formula (III) are those where for R_1 the divalent linking group $-(L_1)-$ is a group represented by any one of the following formulae (Ia), (Ib), (Ic), (Id), (Ie), or (If):


, (Ia)

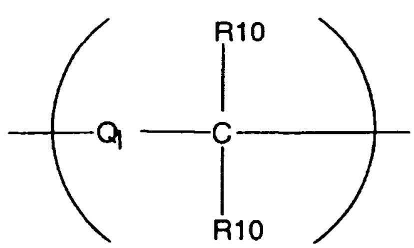

, (Ib)


, (Ic)


or (Id)


(Ie)

or

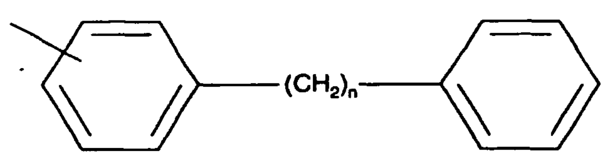

(If)

where Q_1 is a bond or any of the divalent groups (Ia), (Ib), (Ic), (Id), (Ie), and (If) and each R_{10} is

independently hydrogen, C_{1-8} alkyl, C_{1-8} haloalkyl or C_{1-8} alkoxy.

Particularly preferred as the linking group $-(L_1)-$ of R_1 is an alkylene chain of 1 or 2 carbon atoms, namely, $-(CH_2)-$ or $-(CH_2-CH_2)-$.

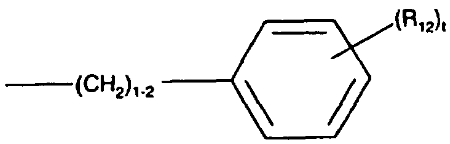
The preferred group for R_{11} is a substituted or unsubstituted group selected from the group consisting of C_5-C_{14} cycloalkyl, C_5-C_{14} cycloalkenyl, phenyl, naphthyl, norbornanyl, bicycloheptadienyl, tolulyl, xylenyl, indenyl, stilbenyl, terphenylyl, diphenylethylenyl, phenyl-cyclohexenyl, acenaphthylenyl, and anthracenyl, biphenyl, bibenzylyl and related bibenzylyl homologues represented by the formula (a);



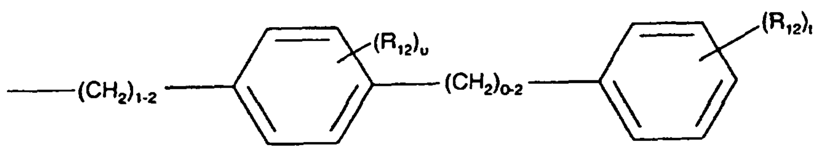
(a)

where n is a number from 1 to 8.

Particularly preferred are compounds wherein for R_1 the combined group $-(L_1)-R_{11}$ is selected from the group consisting of

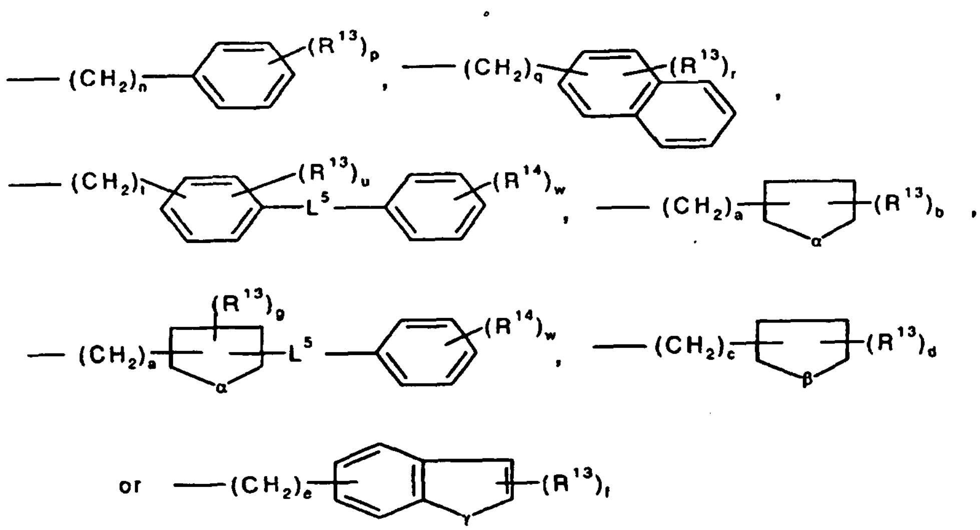


or



where R_{12} is a radical independently selected from halo, C_1-C_8 alkyl, C_1-C_8 alkoxy, -S-(C_1-C_8 alkyl), -O-(C_1-C_8 alkyl) and C_1-C_8 haloalkyl where t is a number from 0 to 5 and u is a number from 0 to 4.

Also preferred for R_{11} is $-(CH_2)m-R^{12}$ wherein m is an integer from 1 to 6, and R^{12} is (d) a group represented by the formula:



wherein a, c, e, n, q, and t are independently an integer from 0 to 2, R^{13} and R^{14} are independently selected from a halogen, C_1 to C_8 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 alkylthio, aryl, heteroaryl, and C_1 to C_8 haloalkyl, α is an oxygen atom or a sulfur atom, L^5 is a bond, $-(CH_2)v-$,

-C=C-, -CC-, -O-, or -S-, v is an integer from 0 to 2, β is $-CH_2-$ or $-(CH_2)_2-$, γ is an oxygen atom or a sulfur atom, b is an integer from 0 to 3, d is an integer from 0 to 4, f, p, and w are independently an integer from 0 to 5, r is an integer from 0 to 7, and u is an integer from 0 to 4, or is (e) a member of (d) substituted with at least one substituent selected from the group consisting of C_1 to C_6 alkyl, C_1 to C_8 alkyloxy, C_1 to C_8 haloalkyloxy, C_1 to C_8 haloalkyl, aryl, and a halogen.

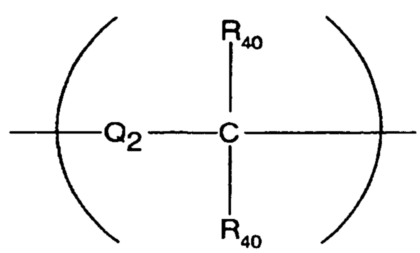
Preferred R_2 substituents:

R_2 is preferably selected from the group consisting of hydrogen, C_1-C_4 alkyl, C_2-C_4 alkenyl, -O-(C_1-C_3 alkyl),

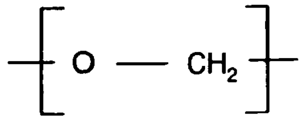
-S-(C_1-C_3 alkyl), -C_3-C_4 cycloalkyl $-CF_3$, halo, $-NO_2$, -CN, $-SO_3$. Particularly preferred R_2 groups are selected from hydrogen, methyl, ethyl, propyl, isopropyl, cyclopropyl, -F, $-CF_3$, -Cl, -Br, or $-O-CH_3$.

Preferred R_4 substituents:

Another preferred subclass of compounds of formula (III) are those wherein R_4 is a substituent having an acylamino acid linker with an acylamino acid linker length of 2 or 3 and the acylamino acid linker group, -(L_C)-, for R_4 is selected from a group represented by the formula;



where Q_2 is selected from the group -(CH_2)-, -O-, -NH-, -C(O)-, and -S-, and each R_{40} is independently selected from hydrogen, C_1-C_8 alkyl, aryl, C_1-C_8 alkaryl, C_1-C_8 alkoxy, aralkyl, and halo. Most preferred are compounds where the acylamino acid linker, -(L_C)-, for R_4 is selected from the specific groups;



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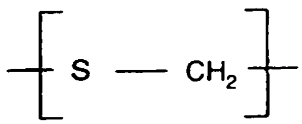

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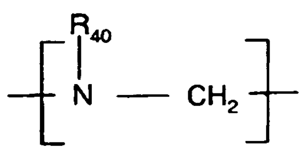

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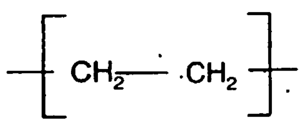

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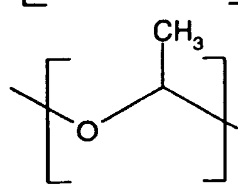
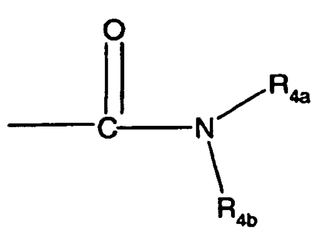


,

where R_{40} is hydrogen or C_1 -C_8 alkyl.

Preferred as the (acylamino acid group) in the group R_4 is the group:



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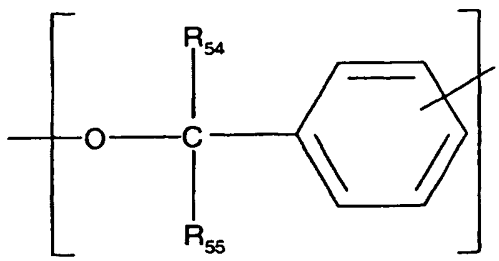
wherein R^{4a} is selected from the group consisting of H, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, heteroaryl and aryl; and wherein NR^{4b} is an amino acid residue of either a natural or unnatural amino acid with the nitrogen atom being part of the amino group of the amino acid. A preferred R^{4a} group is the group hydrogen (H). A preferred source of amino acid residue is the amino acid group selected from the group comprising isoleucine, valine, phenylalanine, aspartic acid, leucine, glycine and isomers and derivatives thereof.

A salt or a prodrug derivative of the (acylamino acid group) is also a suitable substituent.

Particularly preferred are R^{4b} groups that combine with the nitrogen atom to represent amino acid groups selected from: glycine, glycine methyl ester, L-alaninie, L-alanine methylester,L-leucine, L-leucine methyl ester, L-aspartic acid, L-aspartic acid dimethyl ester, L-phenyl alanine, L-phenylalanine methyl ester, malonic acid, malonic acid dimethylester, L- valine, L-valine methyl ester, L-isoleucine, L-isoleucine methyl ester, or salt, and derivatives thereof.

Preferred R_5 Substituents:

Preferred acid linker, $-(L_a)-$, for R5 is selected from the group consisting of;



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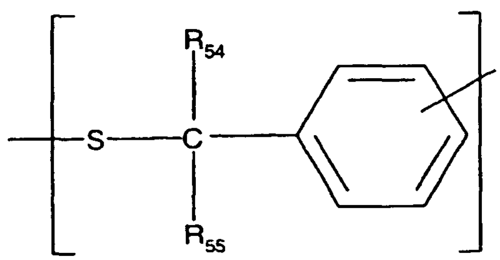

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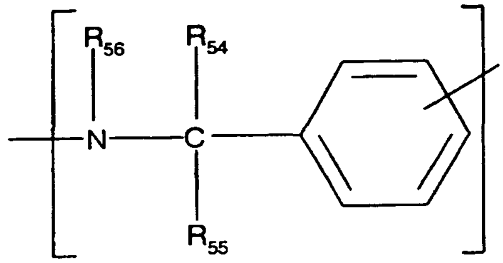

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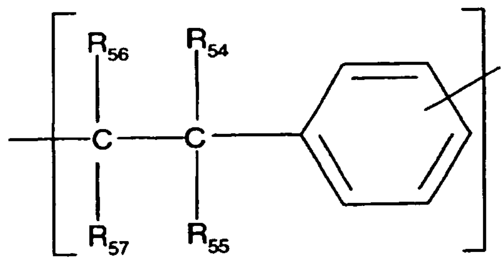

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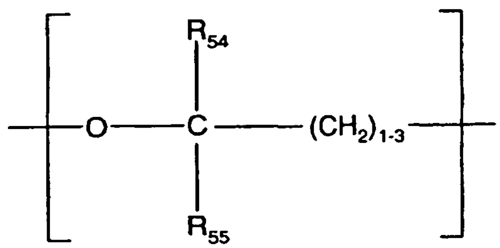

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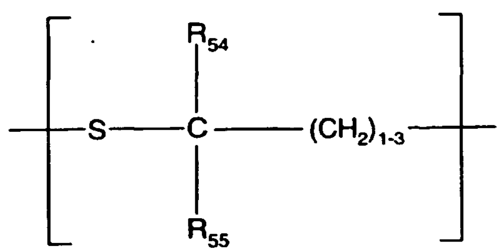

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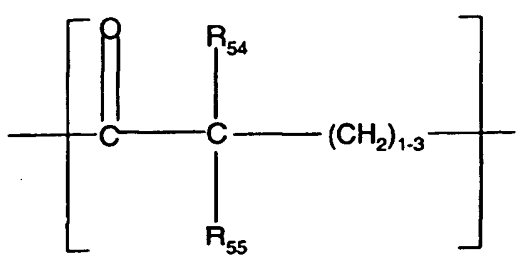

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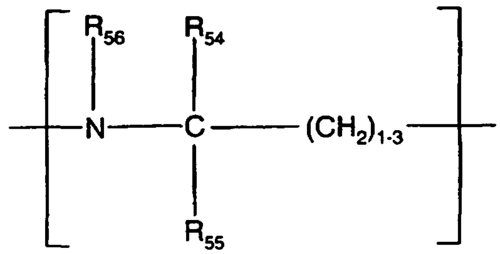

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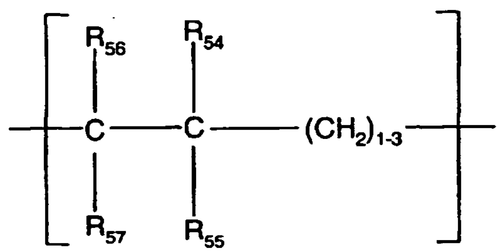

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wherein R_{54}, R_{55}, R_{56} and R_{57} are each independently hydrogen, C_1-C_8 alkyl, C_1-C_8 haloalkyl, aryl, C_1-C_8 alkoxy, or halo. Preferred (acidic group) for R_5 is selected from the group consisting of $-CO_2H$, $-SO_3H$ and $-P(O)(OH)_2$

Preferred R_6 and R_7 substituents:

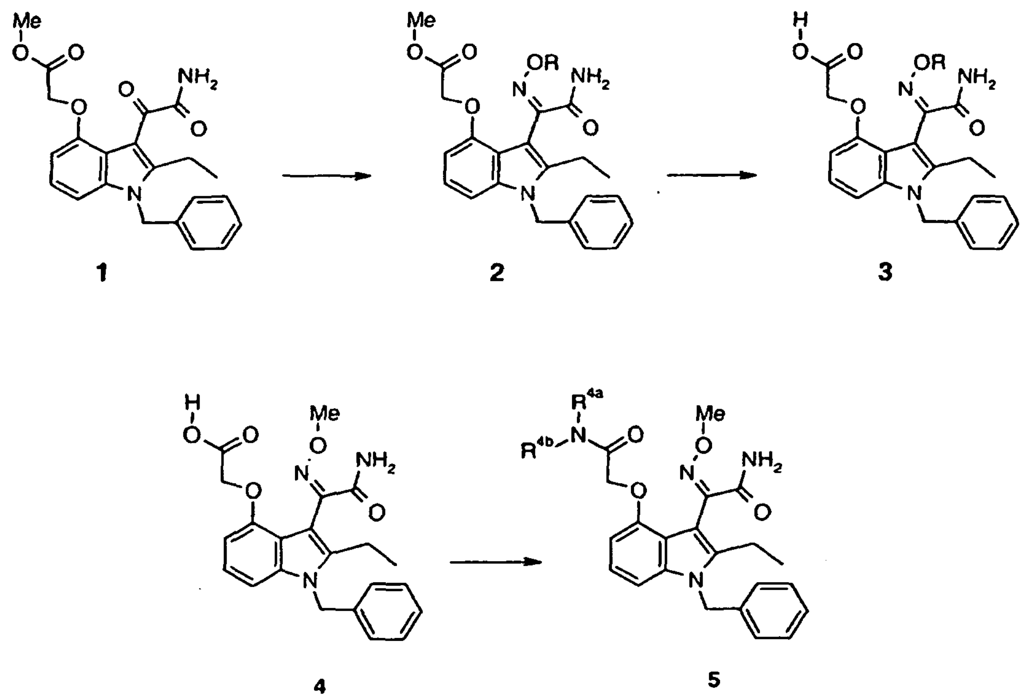
Another preferred subclass of compounds of formula (III) are those wherein for R_6 and R_7 the non-interfering substituent is independently methyl, ethyl, propyl, isopropyl, thiomethyl, -O-methyl, C_4-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_7-C_{12} aralkyl, C_7-C_{12} alkaryl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkenyl, phenyl, tolulyl, xylenyl, biphenyl, C_1-C_6 alkoxy, C_2-C_6 alkenyloxy, C_2-C_6 alkynyloxy, C_2-C_{12} alkoxyalkyl, C_2-C_{12}

alkoxyalkyloxy, C_2-C_{12} alkylcarbonyl, C_2-C_{12} alkylcarbonylamino, C_2-C_{12} alkoxyamino, C_2-C_{12} alkoxyaminocarbonyl, C_1-C_{12} alkylamino, C_1-C_6 alkylthio, C_2-C_{12} alkylthiocarbonyl, C_1-C_6 alkylsulfinyl, C_1-C_6 alkylsulfonyl, C_2-C_6 haloalkoxy, C_1-C_6 haloalkylsulfonyl, C_2-C_6 haloalkyl, C_1-C_6 hydroxyalkyl, -C(O)O(C_1-C_6 alkyl), -$(CH_2)_n$-O-(C_1-C_6 alkyl), benzyloxy, phenoxy, phenylthio, -($CONHSO_2R$), -CHO, amino, amidino, bromo, carbamyl, carboxyl, carbalkoxy, -$(CH_2)_n$-CO_2H, chloro, cyano, cyanoguanidinyl, fluoro, guanidino, hydrazide, hydrazino, hydrazido, hydroxy, hydroxyamino, iodo, nitro, phosphono, -SO_3H, thioacetal, thiocarbonyl, and carbonyl; where n is from 1 to 8.

Most preferred as non-interfering substituents are methyl, ethyl, propyl, and isopropyl.

The indole-3-oxime compounds of the invention can be prepared following protocol of scheme 2 below;

Scheme 2



To introduce the oxime functionality, the methyl ester of the glyoxylamide (compound 10 in scheme 1, compound 1 in scheme 2, *supra.*) is heated with hydroxylamine hydrochloride (when R is H) in a THF/methanol mixture for 8 hours or until the reaction was deemed complete. The reaction product is isolated by chromatography or other known laboratory procedure to afford a white solid. Substituted oximes such as when R is methyl, ethyl, phenyl or other substituent can be prepared by reacting the corresponding substituted hydroxylamine hydrochloride or free base with the

glyoxylamide as described *supra*. The ester functionality at the 4 or 5 position on the indole nucleus, as in for example, compound 2, can be: (a) converted to the acid by hydrolysis using lithium hydroxide or other known ester hydrolysis methods to afford compounds of formula 3, or (b) converted to an amide functionality directly or via the acid functionality to afford compounds of formula 4. General procedures for the conversion of organic acids to amino acid are well known to artisans in the field, and have been documented in general reference texts including, for example, J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985, and R. C. Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989.

The oxime acid compounds of formula 3 such as the methyloxime compound such as that of formula 4 can be converted to the corresponding amino acid derivative via the methylester by coupling with various amino acids by general coupling procedures known to one skilled in the art. Additional references, or procedures are found in J. March Advanced Organic Chemistry, Wiley Interscience publishers, New York, N.Y, 1985; R. C. Larock Comprehensive Organic Transformations, VCH Publishers, New York, N.Y, 1989 and J. Jones Amino Acids and Peptide

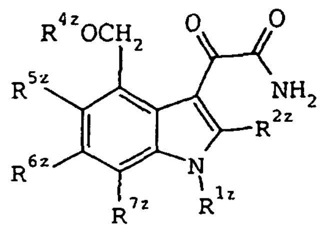
Synthesis, Oxford Science Publications, Stephen G. Davis, Editor, Oxford University Press Inc., New York, NY, 1992.

III. Method of Making the 1H-Indole-3-Glyoxylamide Starting Material for Preparing the Compounds of the Invention:

The synthesis of the indole compounds of the invention (viz., Compounds of Formulae I and II) can be accomplished by well known methods as recorded in the chemical literature. In particular, the indole starting materials may be prepared by the synthesis schemes taught in US Patent No. 5,654,326; the disclosure of which is incorporated herein by reference. Another method of making 1H-indole-3-glyoxylamide $sPLA_2$ inhibitors is described in United States Patent Application Serial No. 09/105381, filed June 26, 1998 and titled, "Process for Preparing 4-substituted 1-H-Indole-3-glyoxyamides" the entire disclosure of which is incorporated herein by reference.

United States Patent Application Serial No. 09/105381 discloses the following process having steps (a) thru (i):

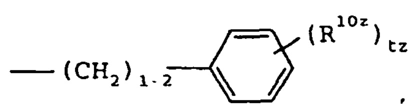
Preparing a compound of the formula (Iz) or a pharmaceutically acceptable salt or prodrug derivative thereof



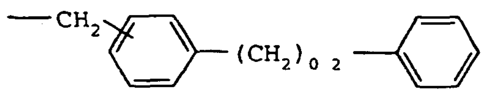
(Iz)

wherein:

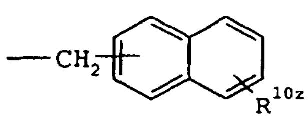
R^{1z} is selected from the group consisting of $-C_7-C_{20}$ alkyl,



,



, and



;

where

R^{10z} is selected from the group consisting of halo, C_1-C_{10} alkyl, C_1-C_{10} alkoxy, $-S-(C_1-C_{10}$ alkyl) and halo(C_1-C_{10})alkyl, and tz is an integer from 0 to 5 both inclusive;

R^{2z} is selected from the group consisting of hydrogen, halo, C_1-C_3 alkyl, C_3-C_4 cycloalkyl, C_3-C_4

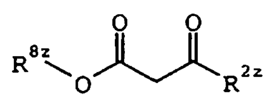
cycloalkenyl, -O-(C_1-C_2 alkyl), -S-(C_1-C_2 alkyl), aryl, aryloxy and HET;

R^{4z} is the group -CO_2H, or salt and prodrug derivative thereof; and

R^{5z}, R^{6z} and R^{7z} are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, halo(C_1-C_6)alkoxy, halo(C_2-C_6)alkyl, bromo, chloro, fluoro, iodo and aryl;

which process comprises the steps of:

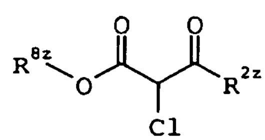
a) halogenating a compound of formula Xz



Xz

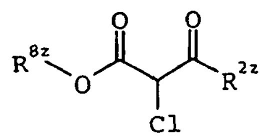
where R^{8z} is (C_1-C_6)alkyl, aryl or HET;

with SO_2Cl_2 to form a compound of formula IX

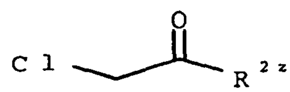


IXz ;

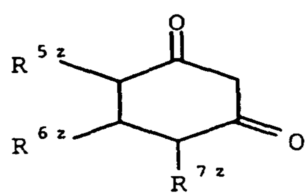
b) hydrolyzing and decarboxylating a compound of formula IXz


IXz

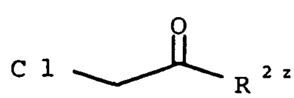
to form a compound of formula VIIIz


VIIIz ;

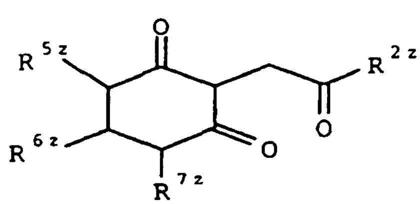
c) alkylating a compound of formula VIIz


VIIz

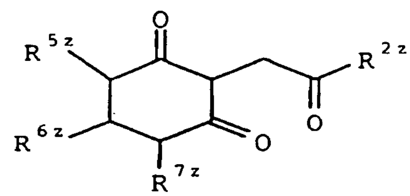
with a compound of formula VIIIz


VIIIz

to form a compound of formula VIz


VIz;

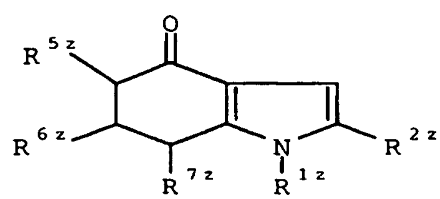
d) aminating and dehydrating a compound of formula VIz



VIz

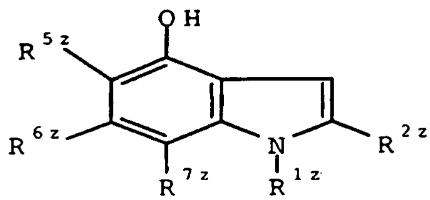
with an amine of the formula $R^{1z}NH_2$ in the presence of a solvent that forms and azeotrope with water to form a compound of formula Vz;

e) oxidizing a compound of formula Vz



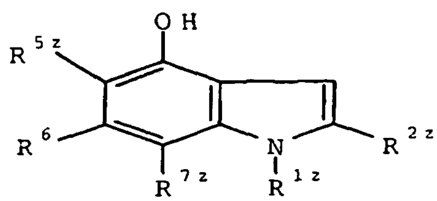
Vz

by refluxing in a polar hydrocarbon solvent having a boiling point of at least 150 °C and a dielectric constant of at least 10 in the presence of a catalyst to form a compound of formula IVz



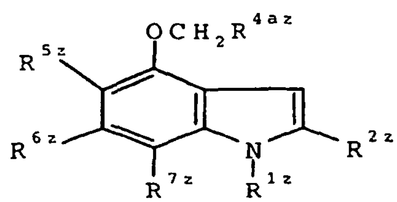
IVz;

f) alkylating a compound of the formula IVz



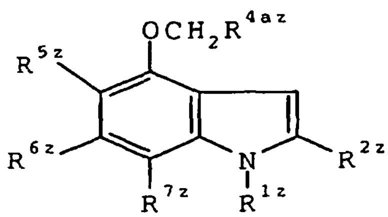
IVz

with an alkylating agent of the formula XCH_2R^{4az} where X is a leaving group and R^{4az} is $-CO_2R^{4b}$, where R^{4bz} is an acid protecting group to form a compound of formula IIIz



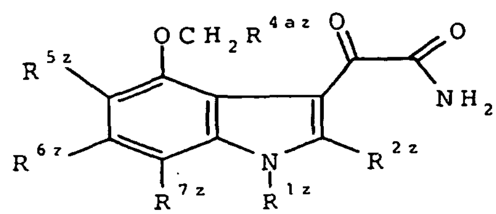
IIIz ;

g) reacting a compound of formula IIIz



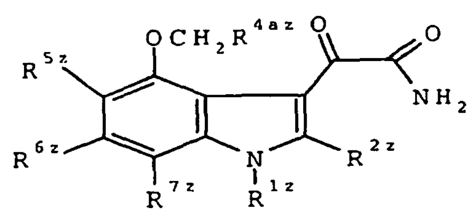
IIIz

with oxalyl chloride and ammonia to form a compound of formula IIz



IIz; and

h) optionally hydrolyzing a compound of formula IIz

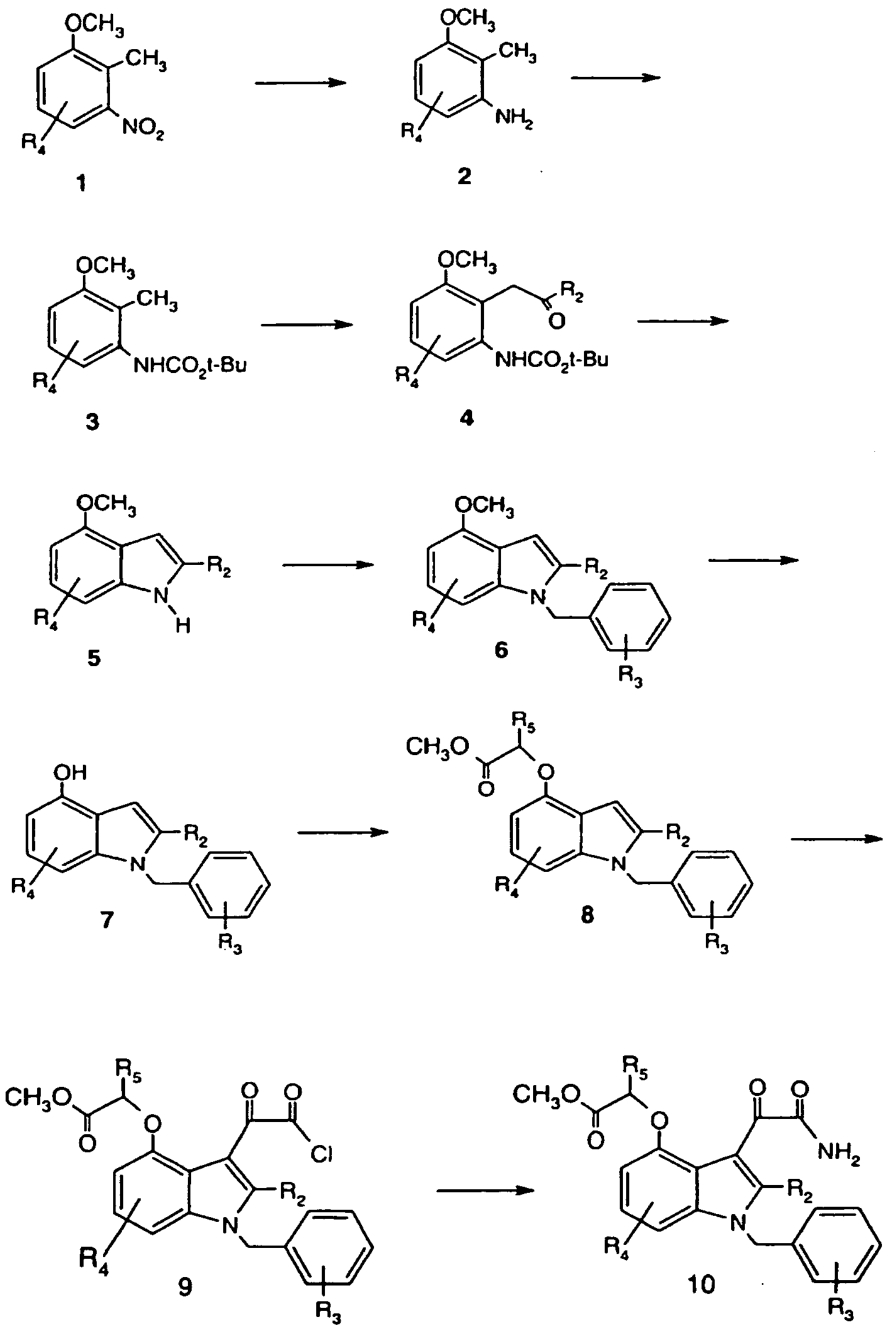


IIz

to form a compound of formula Iz.

An alternative protocol useful for the synthesis of the starting material is shown in Scheme 1 below:

Scheme 1



The synthesis of indole-3-oxime amides (compound of formula I and II, supra.) of this invention uses

as starting material the glyoxamide ((3-(2-amino-1,2-dioxoethyl)-2-methyl-1-(phenylmethyl)-1H-indol-4-yl)oxy)acetic acid methyl ester, compound 10, *supra*. This starting material is prepared as set out in the preceding section or by the method of Example 9 of U.S. Patent No. 5,654,326 (the disclosure of which is incorporated herein by reference).

To obtain the glyoxylamide starting material substituted in the 4-position with an (acidic group) linked through an oxygen atom, the reactions outlined in the scheme *supra*, are used (for conversions 1 through 5, see ref. Robin D. Clark, Joseph M. Muchowski, Lawrence E. Fisher, Lee A. Flippin, David B. Repke, Michel Souchet, *Synthesis*, 1991, 871-878, the disclosures of which are incorporated herein by reference). The starting material ortho-nitrotoluene, 1, is readily reduced to 2-methyl,3-methoxyaniline, 2. Reduction of 1 is by the catalytic hydrogenation of the corresponding nitrotoluene using palladium on carbon as catalyst. The reduction can be carried out in ethanol or tetrahydrofuran (THF) or a combination of both, using a low pressure of hydrogen. The aniline 2, obtained, is converted to the N-tert-butyloxycarbonyl derivative 3, in good yield, on heating with di-tert-butyl dicarbonate in THF at reflux temperature. The dilithium salt of the dianion of 3 is

generated at -40 to -20°C in THF using sec-butyllithium and reacted with the appropriately substituted N-methoxy-N-methylalkanamide to form the ketone 4. This product (4) may be purified by crystallization from hexane, or reacted directly with trifluoroacetic acid in methylene chloride to give the 1,3-unsubstituted indole 5. The 1,3-unsubstituted indole 5 is reacted with sodium hydride in dimethylformamide at room temperature (20-25°C) for 0.5-1.0 hour. The resulting sodium salt of 5 is treated with an equivalent of arylmethyl halide and the mixture stirred at a temperature range of 0-100°C, usually at ambient room temperature, for a period of 4 to 36 hours to give the 1-arylmethylindole, 6. This indole, 6, is O-demethylated by stirring with boron tribromide in methylene chloride for approximately 5 hours (see ref. Tsung-Ying Shem and Charles A Winter, *Adv. Drug Res.*, 1977, 12, 176, the disclosure of which is incorporated herein by reference). The 4-hydroxyindole, 7, is alkylated with an alpha bromoalkanoic acid ester in dimethylformamide (DMF) using sodiumhydride as a base, with reaction condition of 5 to 6. The α-[(indol-4-yl)oxy]alkanoic acid ester, 8, is reacted with oxalyl chloride in methylene chloride to give 9, which is not purified but reacted directly with ammonia to give the glyoxamide 10.

Glyoxamide starting material compounds substituted at the 5 position of the indole nucleus with an (acidic group) may be prepared by methods and starting materials shown in schemes 2 and 3 of Patent No. 5,654,326; the disclosure of which is incorporated herein by reference.

IV. Methods of Using the Compounds of the Invention:

The indole compounds described herein are believed to achieve their beneficial therapeutic action principally by direct inhibition of mammalian (including human) $sPLA_2$, and not by acting as antagonists for arachidonic acid, nor other active agents below arachidonic acid in the arachidonic acid cascade, such as 5-lipoxygenases, cyclooxygenases, and etc.

The method of the invention for inhibiting $sPLA_2$ mediated release of fatty acids comprises contacting mammalian $sPLA_2$ with an therapeutically effective amount of indole compounds corresponding to Formulae (I) or (II) as described herein including salt or a prodrug derivative thereof.

Another aspect of this invention is a method for treating Inflammatory Diseases such as inflammatory bowel disease, septic shock, adult respiratory distress

syndrome, pancreatitis, trauma, bronchial asthma, allergic rhinitis, rheumatoid arthritis, osteoarthritis, and related diseases which comprises administering to a mammal (including a human) a therapeutically effective dose of the indole compound of the invention (see, formulae I and II).

As previously noted the compounds of this invention are useful for inhibiting $sPLA_2$ mediated release of fatty acids such as arachidonic acid. By the term, "inhibiting" is meant the prevention or therapeutically significant reduction in release of $sPLA_2$ initiated fatty acids by the compounds of the invention. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The specific dose of a compound administered according to this invention to obtain therapeutic or prophylactic effects will, of course, be determined by the particular circumstances surrounding the case, including, for example, the compound administered, the route of administration and the condition being treated. Typical daily doses will contain a non-toxic dosage level of from

about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound of this invention.

Preferably compounds of the invention (per Formula I or II) or pharmaceutical formulations containing these compounds are in unit dosage form for administration to a mammal. The unit dosage form can be a capsule or tablet itself, or the appropriate number of any of these. The quantity of Active ingredient in a unit dose of composition may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved. It may be appreciated that it may be necessary to make routine variations to the dosage depending on the age and condition of the patient. The dosage will also depend on the route of administration.

The compound can be administered by a variety of routes including oral, aerosol, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal.

Pharmaceutical formulations of the invention are prepared by combining (e.g., mixing) a therapeutically effective amount of the indole compound of the invention together with a pharmaceutically acceptable carrier or diluent therefor. The present pharmaceutical

formulations are prepared by known procedures using well known and readily available ingredients.

In making the compositions of the present invention, the Active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, semi-solid or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing, for example, up to 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration.

For the pharmaceutical formulations any suitable carrier known in the art can be used. In such a formulation, the carrier may be a solid, liquid, or mixture of a solid and a liquid. For example, for intravenous injection the compounds of the invention may be dissolved in at a concentration of 2 mg/ml in a 4% dextrose/0.5% Na citrate aqueous solution. Solid form formulations include powders, tablets and capsules. A solid carrier can be one or more substances which may also

act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

Tablets for oral administration may contain suitable excipients such as calcium carbonate, sodium carbonate, lactose, calcium phosphate, together with disintegrating agents, such as maize, starch, or alginic acid, and/or binding agents, for example, gelatin or acacia, and lubricating agents such as magnesium stearate, stearic acid, or talc.

In powders the carrier is a finely divided solid which is in admixture with the finely divided Active ingredient. In tablets the Active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 1 to about 99 weight percent of the Active ingredient which is the novel compound of this invention. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar lactose, pectin, dextrin, starch, gelatin, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, low melting waxes, and cocoa butter.

Sterile liquid form formulations include suspensions, emulsions, syrups and elixirs.

The Active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both. The Active ingredient can often be dissolved in a suitable organic solvent, for instance aqueous propylene glycol. Other compositions can be made by dispersing the finely divided Active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

The following pharmaceutical formulations 1 thru 8 are illustrative only and are not intended to limit the scope of the invention in any way. "Active ingredient", refers to a compound according to Formula (I) or (II) or a pharmaceutically acceptable salt, solvate, or prodrug thereof.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantity (mg/capsule)
Active ingredient	250
Starch, dried	200
Magnesium stearate	10
Total	460 mg

Formulation 2

A tablet is prepared using the ingredients below:

	Quantity (mg/tablet)
Active ingredient	250
Cellulose, microcrystalline	400
Silicon dioxide, fumed	10
Stearic acid	5
Total	665 mg

The components are blended and compressed to form tablets each weighing 665 mg

Formulation 3

An aerosol solution is prepared containing the following components:

	Weight
Active ingredient	0.25
Ethanol	25.75
Propellant 22 (Chlorodifluoromethane)	74.00
Total	100.00

The active compound is mixed with ethanol and the mixture added to a portion of the propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and

diluted with the remainder of the propellant. The valve units are then fitted to the container.

Formulation 4

Tablets, each containing 60 mg of Active ingredient, are made as follows:

Active ingredient	60 mg
Starch	45 mg
Microcrystalline cellulose	35 mg
Polyvinylpyrrolidone (as 10% solution in water)	4 mg
Sodium carboxymethyl starch	4.5 mg
Magnesium stearate	0.5 mg
Talc	1 mg
Total	150 mg

The Active ingredient, starch and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The aqueous solution containing polyvinylpyrrolidone is mixed with the resultant powder, and the mixture then is passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

Formulation 5

Capsules, each containing 80 mg of Active ingredient, are made as follows:

Active ingredient	80 mg
Starch	59 mg
Microcrystalline cellulose	59 mg
Magnesium stearate	2 mg
Total	200 mg

The Active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 mesh U.S. sieve, and filled into hard gelatin capsules in 200 mg quantities.

Formulation 6

Suppositories, each containing 225 mg of Active ingredient, are made as follows:

Active ingredient	225 mg
Saturated fatty acid glycerides	2,000 mg
Total	2,225 mg

The Active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

Formulation 7

Suspensions, each containing 50 mg of Active ingredient per 5 ml dose, are made as follows:

Active ingredient	50 mg
Sodium carboxymethyl cellulose	50 mg
Syrup	1.25 ml
Benzoic acid solution	0.10 ml
Flavor	q.v.
Color	q.v.
Purified water to total	5 ml

The Active ingredient is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with a portion of the water and added, with stirring. Sufficient water is then added to produce the required volume.

Formulation 8

An intravenous formulation may be prepared as follows:

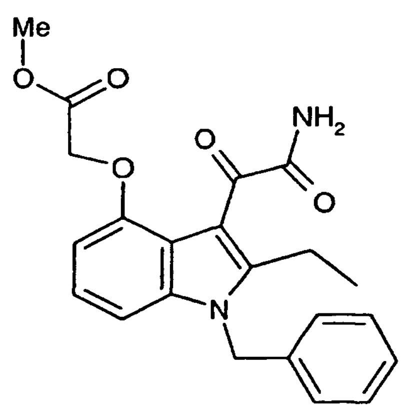
Active ingredient	100 mg
Isotonic saline	1,000 ml

The solution of the above ingredients generally is administered intravenously to a subject at a rate of 1 ml per minute.

All of the products of the Examples described below as well as intermediates used in the following procedures showed satisfactory nmr and IR spectra. They also had the correct mass spectral values.

Example 1

Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester, a compound represented by the compound of formula (1) formula:



(1)

Part A. Preparation of 2-Ethyl-4-methoxy-1H-indole.

A solution of 140 mL (0.18 mol) of 1.3M sec-butyl lithium in cyclohexane was added slowly to N-tert-butoxycarbonyl-3-methoxy-2-methylaniline (21.3g, 0.09 mol)

in 250 mL of THF keeping the temperature below -40°C with a dry ice-ethanol bath. The bath was removed and the temperature allowed to rise to 0°C and then the bath replaced. After the temperature had cooled to -60°C, 18.5g (0.18 mol) of N-methoxy-N-methylpropanamide in an equal volume of THF was added dropwise. The reaction mixture was stirred 5 minutes, the cooling bath removed and stirred an additional 18 hours. It was then poured into a mixture of 300 mL of ether and 400 mL of 0.5N HCl. The organic layer was separated, washed with water, brine, dried over $MgSO_4$, and concentrated at reduced pressure to give 25.5g of a crude of 1-[2-(tert-butoxycarbonylamino)-6-methoxyphenyl]-2-butanone. This material was dissolved in 250 mL of methylene chloride and 50 mL of trifluoroacetic acid and stirred for a total of 17 hours. The mixture was concentrated at reduced pressure and ethyl acetate and water added to the remaining oil. The ethyl acetate was separated, washed with brine, dried ($MgSO_4$) and concentrated. The residue was chromatographed three times on silica eluting with 20% EtOAc/hexane to give 13.9g of 2-ethyl-4-methoxy-1H-indole.

Analyses for $C_{11}H_{13}NO$:

Calculated:	C, 75.40; H, 7.48; N, 7.99
Found:	C, 74.41; H, 7.64; N, 7.97.

<u>Part B.</u> Preparation of 2-Ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.

2-Ethyl-4-methoxy-1H-indole (4.2g, 24 mmol) was dissolved in 30 mL of DMF and 960mg (24 mmol) of 60% NaH/minerial oil was added. After 1.5 hours, 2.9 mL(24 mmol) of benzyl bromide was added. After 4 hours, the mixture was diluted with water and extracted twice with ethyl acetate. The combined ethyl acetate was washed with brine, dried ($MgSO_4$) and concentrated at reduced pressure. The residue was chromatographed on silica gel and eluted with 20% EtOAc/hexane to give 3.1g (49% yield) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole.

Part C. Preparation of 2-Ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole.

3.1g (11.7 mmol) of 2-ethyl-4-methoxy-1-(phenylmethyl)-1H-indole was O-demethylated by treating it with 48.6 mL of 1M BBr_3 in methylene chloride with stirring at room temperature for 5 hours, followed by concentration at reduced pressure. The residue was dissolved in ethyl acetate, washed with brine and dried ($MgSO_4$). After concentrating at reduced pressure, the residue was chromatographed on silica gel eluting with 20% EtOAc/hexane to give 1.58g (54% yield) of 2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole, mp, 86-90°C.

Analyses for $C_{17}H_{17}NO$:

Calculated:	C, 81.24; H, 6.82; N, 5.57
Found:	C, 81.08; H, 6.92; N, 5.41.

Part D. Preparation of [[2-Ethyl-1-(phenylmethyl)-

1H-indol-4-yl]oxy]acetic acid methyl ester.

2-ethyl-4-hydroxy-1-(phenylmethyl)-1H-indole (1.56g, 6.2 mmol) was added to a mixture of 248mg (6.2 mmol) of 60% NaH/mineral oil in 20mL DMF and stirred for 0.67 hour.

Then 0.6 mL(6.2 mmol) of methyl bromoacetate was added and stirring was continued for 17 hours. The mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried ($MgSO_4$), and concentrated at reduced pressure. The residue was chromatographed on silica gel eluting with 20% EtOAc/hexane, to give 1.37g (69% yield) of [[2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester, 89-92°C.

Analyses for $C_{20}H_{21}NO_3$:

Calculated:	C, 74.28; H, 6.55; N, 4.33
Found:	C, 74.03; H, 6.49; N, 4.60.

Part E. **Preparation of [[3-(2-Amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.**

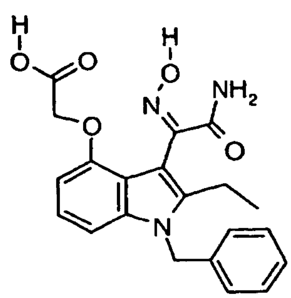
Oxalyl chloride (0.4 mL, 4.2 mmol) was added to 1.36g (4.2 mmol) of [[2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester in 10 mL of methylene chloride and the mixture stirred for 1.5 hours. The mixture was concentrated at reduced pressure and residue taken up in 10 mL of methylene chloride. Anhydrous ammonia was bubbled in for 0.25 hours, the mixture stirred

for 1.5 hours and evaporated at reduced pressure. The residue was stirred with 20 mL of ethyl acetate and the mixture filtered. The filtrate was concentrated to give 1.37g of a mixture of [[3-(2-amino-1,2-dioxoethyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester and ammonium chloride. This mixture melted at 172-187°C.

Example 2

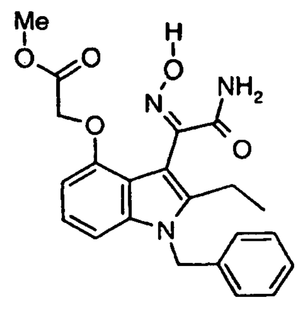
(indol-3-oxime amide starting material)

2-[[3-[[2-(Aminooxo)-1-(*N*-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid.



3ai

A. Preparation of 2-[[3-[[2-(Aminooxo)-1-(*N*-hydroxyimino)]ethyl]-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetic acid methyl ester.



2ai

A stirred mixture of **1** (600 mg, 1.52 mmol) and hydroxylamine hydrochloride (528 mg, 7.60 mmol) in THF (4 mL)/CH_3OH (4 mL) was heated at 55 °C for 8 h. After concentration at ambient temperature, the residue was chromatographed on silica (gradient 0-40% EtOAc in CH_2Cl_2) to give the title compound 2ai (285 mg) as a white solid in 46% yield. IR ($CHCl_3$) 3510, 3415, 1757, 1667 cm^{-1}; ^1H-NMR ($CDCl_3$) δ 1.17 (t, J = 7.5 Hz, 3H), 2.84 (q, J = 7.5 Hz, 2H), 3.81 (s, 3H), 4.73 (s, 2H), 5.36 (s, 2H), 5.67 (br s, 1H), 6.31 (br s, 1H), 6.41 (d, J = 7.8 Hz, 1H), 6.87 (d, J = 8.2 Hz, 1H), 6.98-7.07 (m, 3H), 7.23-7.32 (m, 3H); ESIMS *m/e* 410 (M^++1).

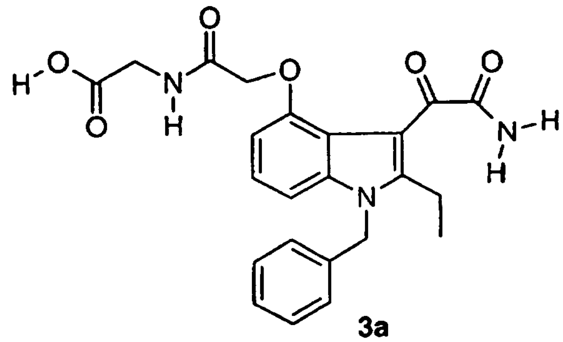
Elemental Analyses for $C_{22}H_{23}N_3O_5 \cdot 0.30(H_2O)$:

Calculated: C, 63.70; H, 5.73; N, 10.13;

Found: C, 63.68; H, 5.62; N, 10.20.

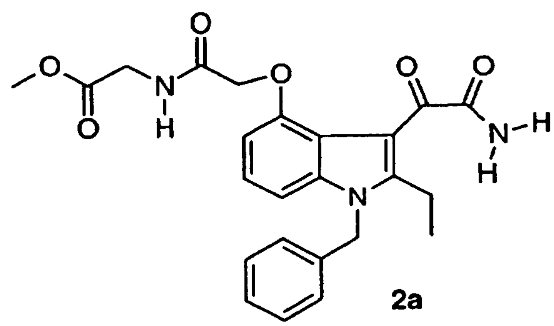
Example 3

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine



3a

A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine methyl ester

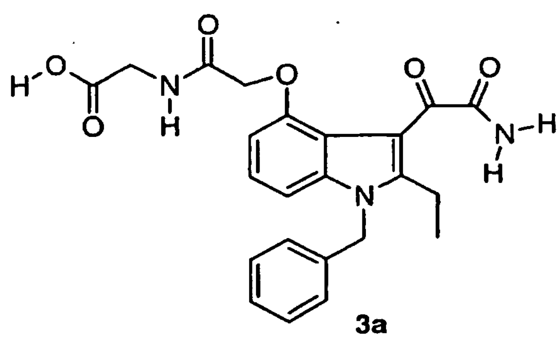


2a

To a solution of **1** (0.100 g, 0.249 mmol) in 2 mL DMF was added collidine (0.069 mL, 0.523 mmol), methyl glycine hydrochloride (0.0313 g, 0.249 mmol), and benzotriazolyl-*N*-oxy-tris(dimethylamino)phosphonium hexafluorophosphate (0.115 g, 0.261) sequentially at room temperature. After 2.5 hrs. the reaction mixture was concentrated *in vacuo* to near dryness, then it was taken up in CH_2Cl_2, chromatographed on a silica gel column (gradient 20-40% THF in CH_2Cl_2) and dried in an 80°C vacuum oven to give 0.0768 g of 2a as a yellow solid in 68% yield. ^{1}H NMR (DMSO-d_6) δ 1.04 (t, *J* = 6.8 Hz, 3H), 2.90 (br q, *J* = 6.8 Hz, 2H),

3.57 (s, 3H), 3.88 (d, J = 5.5 Hz, 2H), 4.57 (s, 2H), 5.51 (s, 2H), 6.59 (d, J = 5.6 Hz, 1H), 7.01-7.08 (m 4H), 7.19-7.30 (m, 3H), 7.55 (s, 1H), 7.99 (s, 1H), 8.40 (t, J = 5.5 Hz, 1H).

B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]glycine



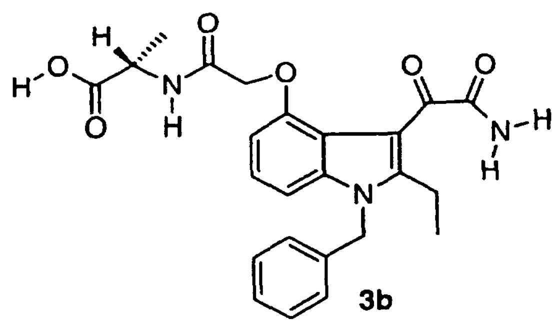
3a

To a solution of 2a (0.035 g, 0.078 mmol) in 1 mL THF, 1 mL MeOH and 0.25 mL distilled H_2O was added 4.17N LiOH (0.093 mL, 0.388 mmol) at room temperature. After 2 hrs. the reaction mixture was acidified with 5N HCl (0.093 mL, 0.465 mmol) and concentrated *in vacuo*. The residue was taken up in CH_2Cl_2 then rapidly triturated with hexanes to give a yellow suspension which was filtered and dried in an 80°C vacuum oven to give 0.0336 g of 3a as a yellow solid in 99% yield. ^1H NMR (DMSO-d_6) δ 1.04 (t, J = 5.9 Hz, 3H), 2.90 (br q, J = 5.9 Hz, 2H), 3.80 (d, J = 4.8 Hz, 2H), 4.56 (s, 2H), 5.51 (s, 2H), 6.62 (d, J = 5.8 Hz, 1H),

7.01-7.28 (m, 7H), 7.54 (s, 1H), 7.99 (s, 1H), 8.31 (t, J = 4.8 Hz, 1H), 12.25-12.75 (br s, 1H).

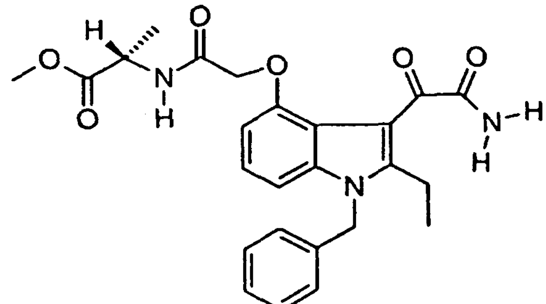
Example 4

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine



3b

A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine methyl ester



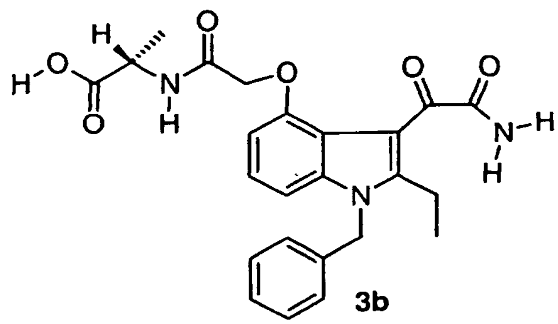
2b

Following the experimental procedure as described for 2a, 2b was obtained as a yellow solid in 65% yield.

^{1}H NMR (DMSO-d_6) δ 1.04 (t, J = 7.2 Hz, 3H), 1.29 (d, J = 7.3 Hz, 3H), 2.91 (br q, J = 7.2 Hz, 2H), 3.54 (s, 3H), 4.29 (qd, J = 7.3, 6.8 Hz, 1H), 4.55 (s, 2H), 5.51 (s,

2H), 6.57 (m, 1H), 6.99 (d, J = 7.4 Hz, 2H), 7.07-7.08 (m, 2H), 7.21-7.31 (m, 3H), 7.56 (s, 1H), 8.05 (s, 1H), 8.40 (d, J = 6.8 Hz, 1H).

B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-alanine

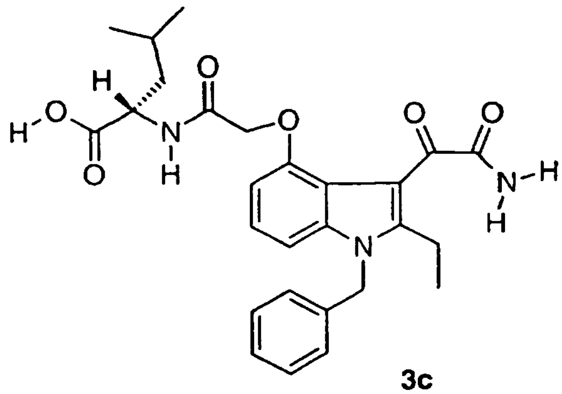


3b

Following the experimental procedure as described for preparing compound 3a, compound 3b, was obtained as a yellow solid in 89% yield. ^{1}H NMR (DMSO-d_6) δ 1.04 (t, J = 7.2 Hz, 3H), 1.29 (d, J = 7.3 Hz, 3H), 2.91 (br q, J = 7.2 Hz, 2H), 4.22 (td, J = 7.2, 7.1 Hz, 1H), 4.54(s, 2H), 5.51 (s, 2H), 6.60 (d, J = 6.3 Hz, 1H), 7.00-7.09 (m, 4H), 7.21-7.30 (m, 3H), 7.53 (s, 1H), 8.03 (s, 1H), 8.31 (d, J = 7.1 Hz, 1H), 12.75-12.84 (br s, 1H).

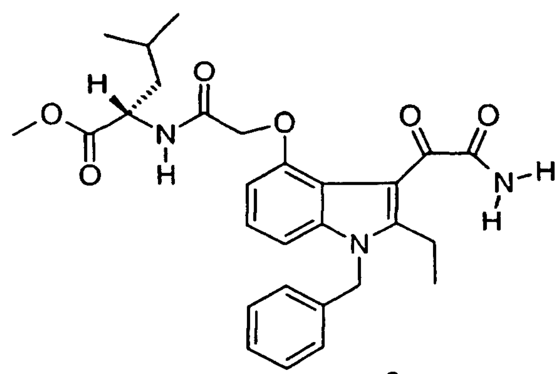
Example 5

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine



3c

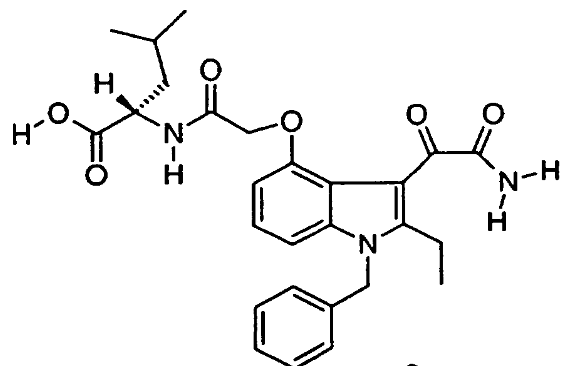
A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine methyl ester



2c

Following the experimental procedure as described for 2a, 2c was obtained as a yellow solid in 98% yield. ^{1}H NMR (DMSO-d_6) δ 0.67 (d, *J* = 5.5 Hz, 3H), 0.72 (d, *J* = 5.7 Hz, 3H), 1.05 (t, *J* = 7.2 Hz, 3H), 1.30-1.50 (m, 2H), 1.51-1.64 (m, 1H), 2.91 (br q, *J* = 7.2 Hz, 2H), 3.55 (s, 3H), 4.20-4.27 (m, 1H), 4.57 (s, 2H), 5.52 (s, 2H), 6.53-6.56 (m, 1H), 6.97-7.08 (m, 4H), 7.21-7.29 (m, 3H), 7.56 (s, 1H), 8.07 (s, 1H), 8.37 (d, *J* = 7.3 Hz, 1H).

B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-leucine

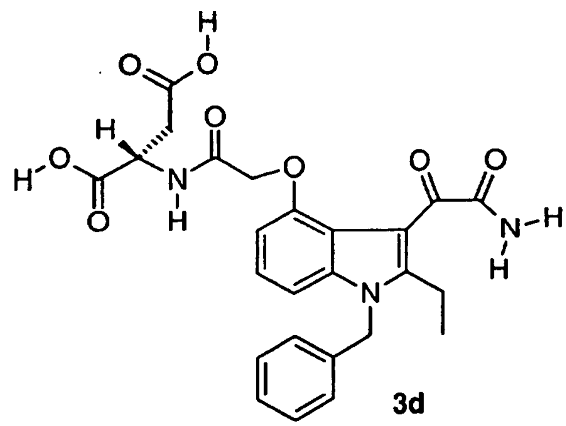


3c

Following the experimental procedure as described for 3a, 3c was obtained as a yellow solid in 75% yield. ^{1}H NMR (DMSO-d_6) δ 0.76 (d, *J* = 5.7 Hz, 3H), 0.78 (d, *J* = 6.1 Hz, 3H), 1.21 (t, *J* = 7.3 Hz, 3H), 1.39-1.43 (m, 1H), 1.69 (t, *J* = 7.3 Hz, 2H), 2.96 (br q, *J* = 7.3 Hz, 2H), 4.57-4.65 (m, 1H), 4.69 (d, *J* = 16.0 Hz, 1H), 4.78 (d, *J* = 16.0 Hz, 1H), 5.38 (s, 2H), 6.59 (d, *J* = 8.0 Hz, 1H), 6.89 (d, *J* = 8.2 Hz,1H), 6.95-7.12 (m, 5H), 7.26-7.32 (m, 3H), 8.17 (d, *J* = 8.2 Hz, 1H).

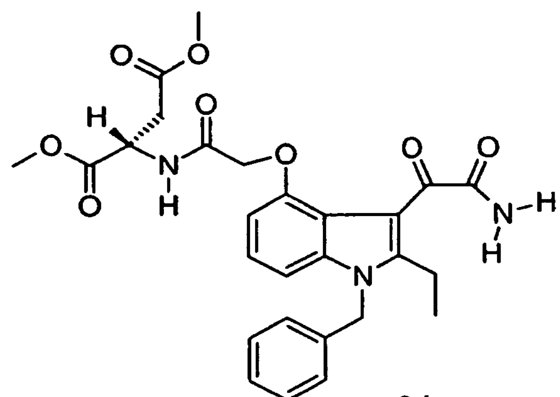
Example 6

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid



3d

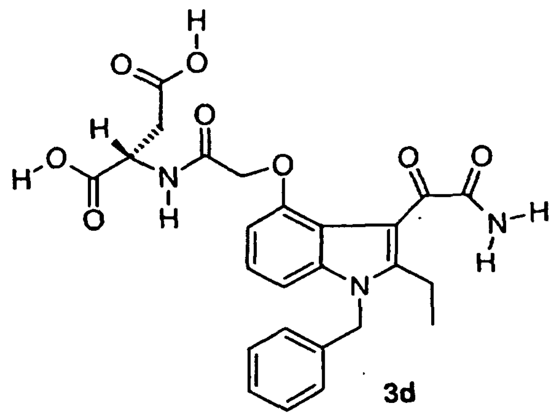
A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid dimethyl ester



2d

Following the experimental procedure as described for 2a, 2d was obtained as a yellow solid in 88% yield. ^{1}H NMR (DMSO-d_6) δ 1.04 (t, J = 7.3 Hz, 3H), 2.72 (dd, J = 16.6, 7.1 Hz, 1H), 2.83 (dd, J = 16.7, 7.1 Hz, 1H), 2.90 (br q, J = 7.3 Hz, 2H), 3.49 (s, 3H), 3.55 (s, 3H), 4.54 (s, 2H), 4.66 (m, 1H), 5.51 (s, 2H), 6.54 (m, 1H), 6.97-7.09 (m, 4H), 7.21-7.30 (m, 3H), 7.50 (s, 1H), 7.97 (s, 1H), 8.52 (d, J = 7.9 Hz, 1H).

B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-aspartic acid

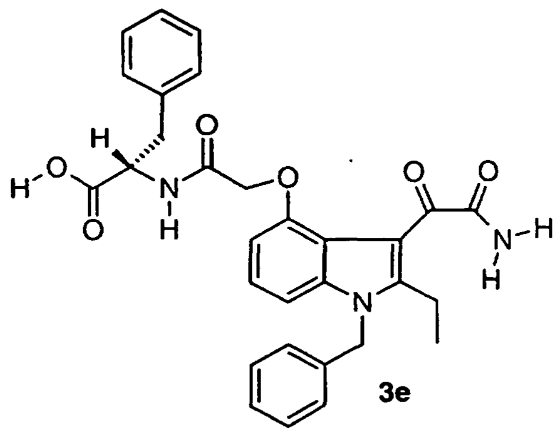


3d

Following the experimental procedure as described for 3a, 3d was obtained as a yellow solid in 99% yield. ^{1}H NMR (DMSO-d_6) δ 1.04 (t, *J* = 7.2 Hz, 3H), 2.52-2.76 (m, 2H), 2.90 (br q, *J* = 7.2 Hz, 2H), 4.53 (s, 2H), 4.53-4.60 (m, 1H), 5.50 (s, 2H), 6.59 (d, *J* = 7.2 Hz, 1H), 6.98-7.09 (m, 4H), 7.19-7.30 (m, 3H), 7.47 (s, 1H), 7.94 (s, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 12.40-13.20 (br s, 2H).

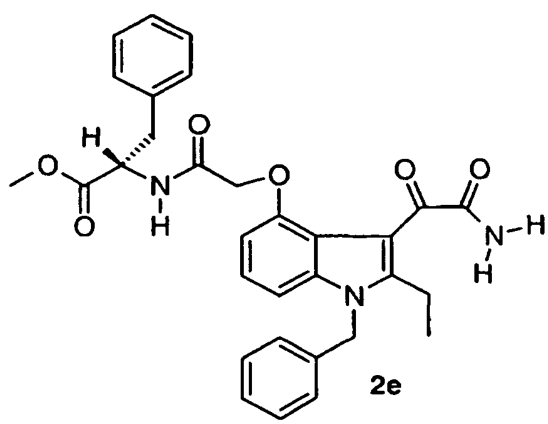
Example 7

N-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine



3e

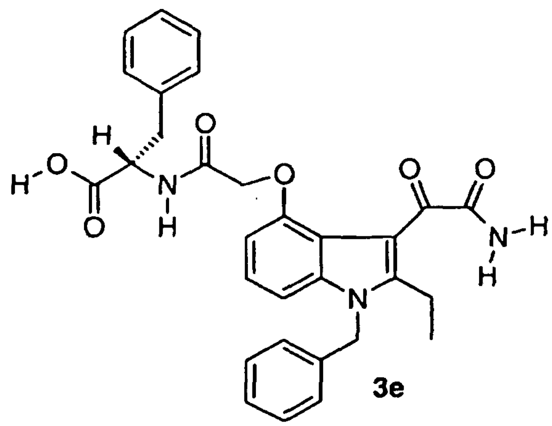
A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine methyl ester



2e

Following the experimental procedure as described for 2a, 2e was obtained as a yellow solid in 68% yield. ^{1}H NMR (DMSO-d_6) δ 1.06 (t, J = 7.2 Hz, 3H), 2.88-3.03 (m, 4H), 3.54 (s, 3H), 4.47-4.50 (m, 1H), 4.50 (s, 2H), 5.52 (s, 2H), 6.41 (d, J = 7.7 Hz, 1H), 6.98-7.11 (m, 9H), 7.21-7.30 (m, 3H), 7.47 (s, 1H), 8.06 (s, 1H), 8.52 (d, J = 7.7 Hz, 1H).

B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-phenylalanine

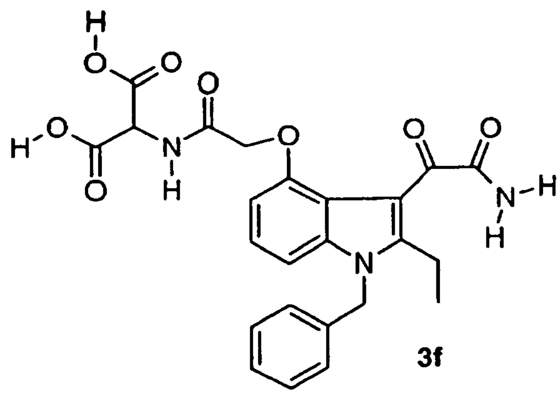


3e

Following the experimental procedure as described for 3a, 3e was obtained as a yellow solid in 93% yield. ^{1}H NMR (DMSO-d_6) δ 1.04 (t, *J* = 7.1 Hz, 3H), 2.85-3.12 (m, 4H), 4.17-4.26 (m, 1H), 4.54 (s, 2H), 5.51 (s, 2H), 6.59 (d, *J* = 6.4 Hz, 1H), 6.98-7.09 (m, 9H), 7.19-7.30 (m, 3H), 7.53 (s, 1H), 8.03 (s, 1H), 8.30 (d, *J* = 7.0 Hz, 1H), 12.50 (br s, 1H).

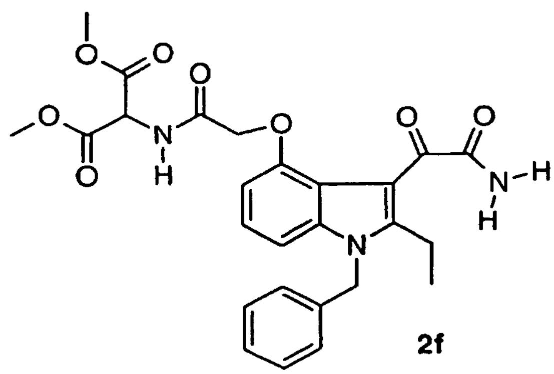
Example 8

[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid



3f

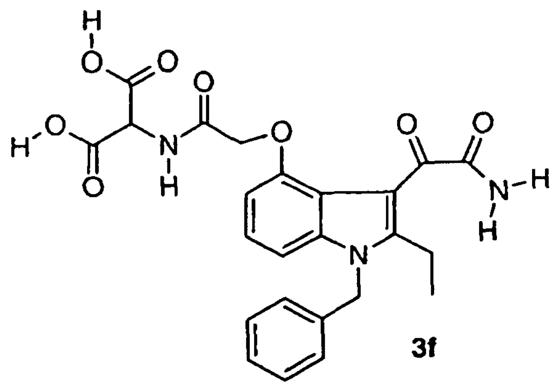
A. Preparation of [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid dimethyl ester



2f

Following the experimental procedure as described for 2a, 2f was obtained as a yellow solid in 98% yield. ^{1}H NMR (DMSO-d_6) δ 1.04 (t, J = 7.3 Hz, 3H), 2.90 (br q, J = 7.3 Hz, 2H), 3.64 (s,6H), 4.63 (s, 2H), 5.16 (d, J = 7.1 Hz, 1H), 5.51 (s, 2H), 6.54-6.56 (m, 1H), 6.98-7.09 (m, 4H), 7.21-7.30 (m, 3H), 7.43 (s,, 1H), 7.88 (s, 1H), 8.90 (d, J = 7.2 Hz, 1H).

B. Preparation of [2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetamido]malonic acid

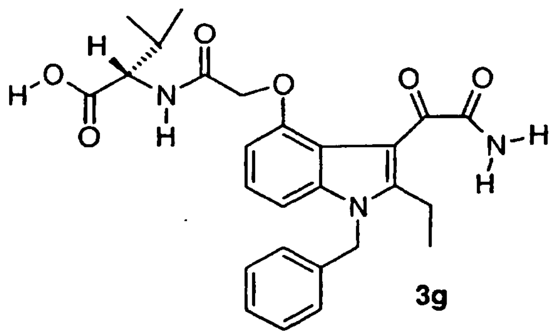


3f

Following the experimental procedure as described for 3a, 3f was obtained as a yellow solid in 99% yield. ^{1}H NMR (DMSO-d_6) δ 1.04 (t, *J* = 6.9 Hz, 3H), 2.89 (br q, *J* = 7.3 Hz, 2H), 4.62 (s, 2H), 4.91 (d, *J* = 7.2 Hz, 1H), 5.50 (s, 2H), 6.57 (d, *J* = 7.2 Hz, 1H), 6.98-7.09 (m, 4H), 7.18-7.30 (m, 3H), 7.37 (s, 1H), 7.83 (s, 1H), 8.55 (d, *J* = 7.2 Hz, 1H), 12.30-13.00 (br s, 2H).

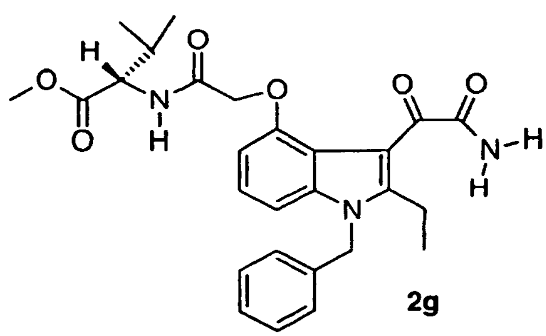
Example 9

***N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-L-valine**



3g

A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-L-valine methyl ester

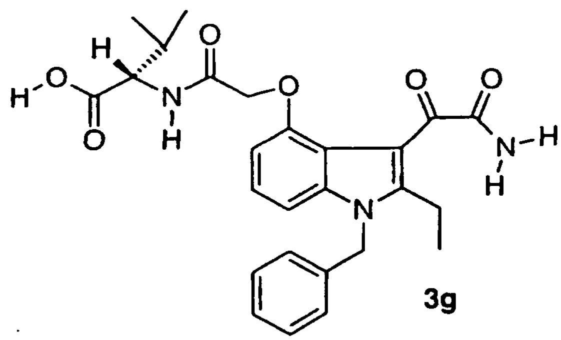


2g

Following the experimental procedure as described for 2a, 2g was obtained as a yellow solid in 96% yield. ^{1}H NMR (DMSO-d_6) δ 0.71 (d, J = 6.8 Hz, 3H), 0.74 (d, J = 7.0 Hz, 3H), 1.05 (t, J = 7.2 Hz 3H), 1.99-2.05 (m, 1H), 2.90 (br q, J = 7.2 Hz, 2H), 3.54 (s, 3H), 4.11 (br t, J = 7.0 Hz, 1H), 4.60 (s, 2H), 5.52 (s, 2H), 6.52 (d, J = 4.4 Hz, 1H),

6.95 (d, J = 7.2 Hz, 2H), 7.06 (br s, 2H), 7.18-7.29 (m, 3H), 7.52 (s, 1H), 8.04 (s, 1H), 8.20 (d, J = 7.8 Hz, 1H).

B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-valine

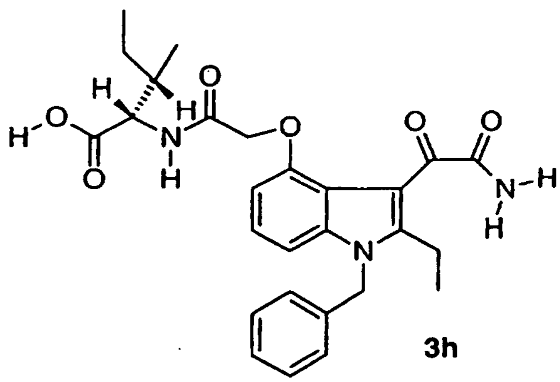


3g

Following the experimental procedure as described for 3a, 3g was obtained as a yellow solid in 94% yield. ^{1}H NMR (DMSO-d_6) δ 0.71 (d, J = 6.9 Hz, 3H), 0.75 (d, J = 6.8 Hz, 3H), 1.04 (t, J = 7.3 Hz 3H), 2.01-2.07 (m, 1H), 2.90 (br q, J = 7.3 Hz, 2H), 4.09 (br dd, J = 7.9, 6.2 Hz, 1H), 4.60 (s, 2H), 5.51 (s, 2H), 6.54 (d, J = 6.1 Hz, 1H), 6.95 (d, J = 7.3 Hz, 2H), 6.99-7.08 (m, 2H), 7.18-7.29 (m, 3H), 7.49 (s, 1H), 8.01 (s, 1H), 8.08 (d, J = 8.2 Hz, 1H), 12.63 (br s, 1H).

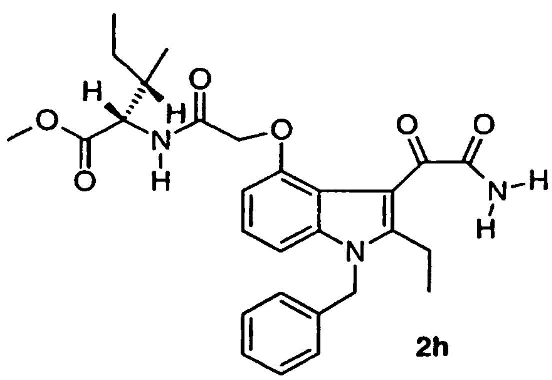
Example 10

***N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-L-isoleucine**



3h

A. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1*H*-indol-4-yl]oxy]acetyl]-L-isoleucine methyl ester

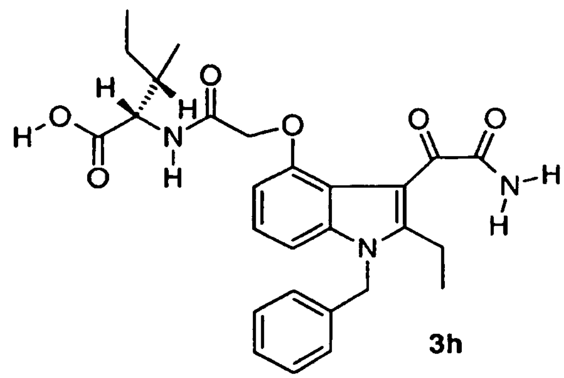


2h

Following the experimental procedure as described for 2a, 2h was obtained as a yellow solid in 73% yield. ^{1}H NMR (DMSO-d_6) δ 0.64-0.71 (m, 6H), 0.99-1.08 (m, 4H), 1.21-1.26 (m, 1H), 1.76-1.80 (m, 1H), 2.91 (br q, J = 7.4 Hz, 2H), 3.53 (s, 3H), 4.15 (br t, J = 7.2 Hz, 1H), 4.60 (s,

2H), 5.52 (s, 2H), 6.52 (m, 1H), 6.96 (d, J = 7.2 Hz, 2H), 7.02-7.07 (m, 2H), 7.18-7.29 (m, 3H), 7.53 (s, 1H), 8.04 (s, 1H), 8.23 (d, J = 7.7 Hz, 1H).

B. Preparation of *N*-[2-[[3-(Aminooxoacetyl)-2-ethyl-1-(phenylmethyl)-1H-indol-4-yl]oxy]acetyl]-L-isoleucine



3h

Following the experimental procedure as described for 3a, 3h was obtained as a yellow solid in 92% yield. ^{1}H NMR (DMSO-d_6) δ 0.64-0.84 (m, 6H), 1.04 (t, J = 7.2 Hz, 3H), 1.21-1.28 (m, 2H), 1.76-1.80 (m, 1H), 2.91 (br q, J = 7.2 Hz, 2H), 4.12 (br t, J = 7.3 Hz, 1H), 4.59 (s, 2H), 5.51 (s, 2H), 6.55 (d, J = 6.4 Hz, 1H), 6.96 (d, J = 7.2 Hz, 2H), 7.01-7.08 (m, 2H), 7.21-7.29 (m, 3H), 7.51 (s, 1H), 8.01 (s, 1H), 8.11 (d, J = 7.4 Hz, 1H), 12.40-12.65 (br s, 1H).

Assay

The following chromogenic assay procedure was used to identify and evaluate inhibitors of recombinant human secreted phospholipase A_2. The assay described herein has been adapted for high volume screening using 96 well microtiter plates. A general description of this assay method is found in the article, "Analysis of Human Synovial Fluid Phospholipase A_2 on Short Chain Phosphatidylcholine-Mixed Micelles: Development of a Spectrophotometric Assay Suitable for a Microtiterplate Reader", by Laure J. Reynolds, Lori L. Hughes, and Edward A Dennis, Analytical Biochemistry, 204, pp. 190-197, 1992 (the disclosure of which is incorporated herein by reference):

Reagents:

REACTION BUFFER -

$CaCl_2 \cdot 2H_2O$ (1.47 g/L)

KCl (7.455 g/L)

Bovine Serum Albumin (fatty acid free) (1 g/L)
(Sigma A-7030, product of Sigma
Chemical Co., St. Louis MO, USA)

TRIS HCl (3.94 g/L)

pH 7.5 (adjust with NaOH)

ENZYME BUFFER -

0.05 $NaOAc.3H_2O$, pH 4.5

0.2 NaCl

Adjust pH to 4.5 with acetic acid

DTNB - 5,5'-dithiobis-2-nitrobenzoic acid

RACEMIC DIHEPTANOYL THIO - PC

racemic 1,2-bis(heptanoylthio)-1,2-dideoxy-*sn*-glycero-3-phosphorylcholine

TRITON X-100™ prepare at 6.249 mg/ml in reaction buffer to equal 10uM.

REACTION MIXTURE -

A measured volume of racemic dipheptanoyl thio PC supplied in chloroform at a concentration of 100 mg/ml is taken to dryness and redissolved in 10 millimolar

TRITON X-100™ nonionic detergent aqueous solution. Reaction Buffer is added to the solution, then DTNB to give the Reaction Mixture.

The reaction mixture thus obtained contains 1mM diheptanoly thio-PC substrate, 0.29 mm Triton X-100™ detergent, and 0.12 mm DTMB in a buffered aqueous solution at pH 7.5.

Assay Procedure:

1. Add 0.2 ml reaction mixture to all wells;
2. Add 10 ul test compound (or solvent blank) to appropriate wells, mix 20 seconds;
3. Add 50 nanograms of $sPLA_2$ (10 microliters) to appropriate wells;

4. Incubate plate at 40 °C for 30 minutes;

5. Read absorbance of wells at 405 nanometers with an automatic plate reader.

All compounds were tested in triplicate. Typically, compounds were tested at a final concentration of 5 ug/ml. Compounds were considered active when they exhibited 40% inhibition or greater compared to uninhibited control reactions when measured at 405 nanometers. Lack of color development at 405 nanometers evidenced inhibition. Compounds initially found to be active were reassayed to confirm their activity and, if sufficiently active, IC_{50} values were determined. Typically, the IC_{50} values (see, Table I, below) were determined by diluting test compound serially two-fold such that the final concentration in the reaction ranged from 45 ug/mL to 0.35 ug/ml. More potent inhibitors required significantly greater dilution. In all cases, % inhibition measured at 405 nanometers generated by enzyme reactions containing inhibitors relative to the uninhibited control reactions was determined. Each sample was titrated in triplicate and result values were averaged for plotting and calculation of IC_{50} values. IC_{50} were determined by plotting log concentration versus inhibition values in the range from 10-90% inhibition.

Results of Human Secreted Phospholipase A_2 Inhibition Tests

Table

Compound No. from Examples 3-10	Inhibition of human secreted PLA_2 IC50 ± mean deviation (3-4 tests)(nM)
1	49
2A	529
2B	533
2C	82
2D	874
2E	666
2F	698
2G	283
2H	166
3A	71
3B	59
3C	28
3D	132
3E	64
3F	44.7
3G	36.4
3H	25.1

The compound of Example 1 is highly active in inhibiting $sPLA_2$.

While the present invention has been illustrated above by certain specific embodiments, it is not intended that these specific examples should limit the scope of the invention as described in the appended claims.